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ION CHANNELS IN HEALTH AND DISEASE

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Preface

This is the first edition of *Ion Channels in Health and Disease*. I am honored to serve as its Editor and grateful to Dr. Michael Conn, the series editor for *Prospectives in Translational Cell Biology*, for his invitation to work on this project. It is an invitation that I readily accepted, since this is the right time to focus on ion channels and disease. Channelopathies, diseases resulting from abnormal channel function, were some of the first and best characterized Mendelian and de novo genetic disorders. Now, with the explosion of new structural information about ion channels, made more accessible by advances in structural biology such as cryoelectron microscopy, and a flood of new genetic information flowing from cheaper and faster sequencing technologies, ion channels and channel dysfunction have entered the spotlight of multiple disease investigations. Simultaneously, as our understanding of ion channel function has matured, there has been an increased focus on the pathophysiology resulting from channel disorders and an increasing recognition that some of our long-accepted paradigms need to be revised. For instance, voltage-gated ion channels (particularly sodium and calcium voltage-gated ion channels) were long considered to function solely in electrically excitable tissues, such as muscle and brain. Recent evidence, however, has demonstrated unexpected roles of these and other channels in cancer and in development of nonexcitable tissues, suggesting even broader functions of these channels. Given these and other new advances, this edition focused on the role of ion channels in health and disease is timely and should be a valuable resource to many. Moreover, ion channels as a class are proven drug targets. Thus, a growing appreciation of the role of ion channels in health and disease provides an opportunity to develop new therapeutic strategies.

The individual chapters, authored by leaders in their fields, demonstrate the broad contributions of ion channels to health and disease. New takes on how ion channels contribute to cardiac arrhythmias or neurological disorders, areas in which channel roles are well established, are provided in chapters from Geoff Abbott; Bill Catterall; Elaine Wan and Steven Marx; Jacy Wagnon, Rosie Bunton-Stasyshyn, and Miriam Meisler; Lucia Romero Perez, Sergei Noskov, and Coleen Clancy; Scott Bernstein and Glenn Fishman; and Najim Lhrouchi and Arthur Wilde. Maria Remedi and Colin Nichols focuses on K_{ATP} channels, the targets of sulfonylureas used to treat diabetes. Roles of channels in cancer, a burgeoning field, are discussed by William Brackenbury. Also, Geoff Abbott's chapter

focuses on how KCNE channel proteins regulate ion transport in the various secretory processes. Amy Hanna, Lydia Sharp, and Susan Hamilton addresses the roles of ryanodine receptor mutations in various muscle diseases, such as malignant hyperthermia, central core disease, and congenital myopathies. Huanghe Yang and Lily Jan provides a review on the on the rapidly expanding roles of a new class of channels, the TMEM16 family, that has now been implicated in multiple disease processes. Melissa Miller, Steven Mansell, and Polina Lishko discusses another novel family of channels, the Catsper channels, and how they control fertility. TingTing Hong and Robin Shaw; Jing Zhai, Qing-Shu Lin, Zhenyu Hu, Ruixiong Wong, and Tuck Wah Soong tackle more general processes, ion channel trafficking and alternative splicing, and how dysregulation contributes to an array of disease processes. Each of these chapters, providing the latest in structural, genetic, and biophysical information, emphasizes the central roles of ion channels in physiology and disease and offer insights into new therapeutic and diagnostic possibilities. I want to sincerely thank each of these authors, and their coauthors, for the thoughtful contributions. This collection will serve as a valuable resource for students, researchers, and physicians interested in this fascinating field.

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CHAPTER

1

The *KCNE* Family of Ion Channel Regulatory Subunits

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INTRODUCTION

The *KCNE* gene family was first recognized in 1988, when Takumi and colleagues fractionated rat kidney mRNA, injected it into *Xenopus laevis* oocytes, and recorded electrical currents from the oocytes using the two-electrode voltage-clamp recording technique. When they clamped oocytes containing a certain fraction of mRNA to depolarized membrane potentials, Takumi et al. recorded very slowly activating, K^+-selective currents. From this fraction, they cloned the *KCNE1* cDNA, which expressed a 130 amino acid, single-pass transmembrane protein they termed IsK (slow K^+ current) and which was later referred to as minK, for minimal K^+ channel.[1,2] Today, IsK is most commonly referred to by its gene nomenclature (KCNE1) for both the gene and its protein product; we will use this system here, italicizing when referring to the gene rather than the protein.

KCNE1 was an enigmatic protein—it was small for a channel gene and possessed no homology with previously cloned channel genes. Mutagenesis studies confirmed that KCNE1 point mutants altered channel properties, alleviating concerns that the results were an artifact. Significantly, currents generated by *KCNE1* RNA injection into oocytes closely resembled the native cardiac slowly activating K^+ (I_{Ks}) current, which also fails to saturate even after several seconds of membrane depolarization at room temperature.[3] But how could this miniscule protein generate this K^+-selective current? The crucial breakthrough came in 1996. In that year, the Keating group reported positional cloning of a gene (KVLQT1) that is strongly expressed in the heart and "encodes a protein with structural features of a voltage-gated potassium channel." They linked KVLQT1 (now usually termed KCNQ1 or Kv7.1) to long QT syndrome (LQTS), a

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potentially lethal ventricular arrhythmia characterized by impaired ventricular repolarization and therefore lengthening of the electrocardiogram (ECG) QT interval[4] (Fig. 1.1A). Later that year, two teams independently reported that KCNE1 does not generate currents on its own, but modifies currents passed by KCNQ1 by coassembling with it to form a heteromeric, voltage-gated potassium (Kv) channel with dramatically altered properties[5,6] (Fig. 1.1B and C).

KCNE1 cRNA injection into *X. laevis* oocytes generates I_{Ks}-like currents because oocytes express endogenous KCNQ1, which is not readily distinguishable from other endogenous oocyte currents until it is upregulated and its activation slowed by exogenous KCNE1.[5–8] KCNE1 was thus

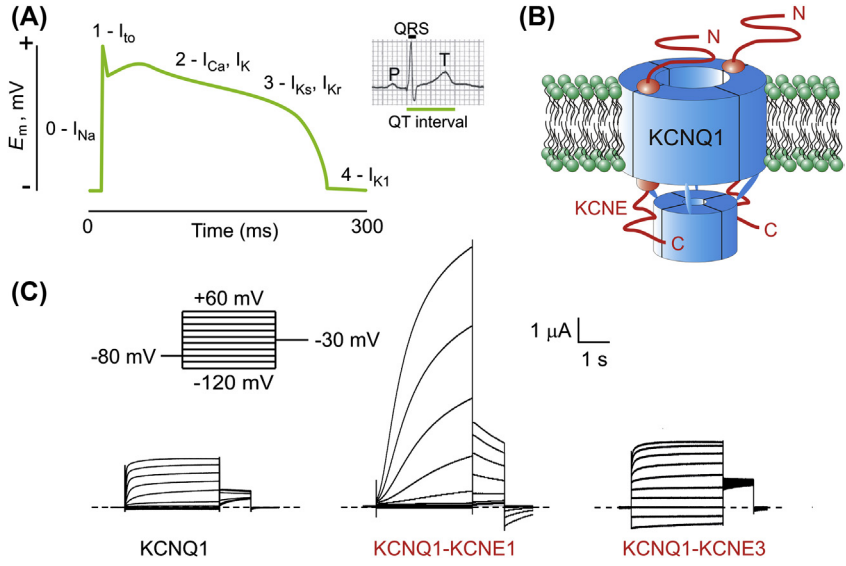

FIGURE 1.1 KCNE regulation of KCNQ1 and cardiac electrophysiology. (A) The upstroke (0) of the human ventricular myocyte action potential is facilitated by Na^+ influx. The initial repolarization notch is caused by the transient outward K^+ current (I_{to}), and the plateau phase (2) is a balance between residual Na^+ current, Ca^{2+} influx, and K^+ efflux (I_K). Phase 3 repolarization is primarily achieved by I_{Ks} (mediated by KCNQ1-KCNE1 and possibly other KCNQ1-KCNE combinations) and I_{Kr}. Inward rectifiers (I_{K1}) help to determine resting membrane potential between action potentials. *Upper right inset:* surface electrocardiogram showing P wave, QRS complex, T wave, and QT interval. (B) Schematic of a KCNQ1-KCNE Kv channel complex. (C) Functional effects of KCNE1 and KCNE3 on KCNQ1. KCNQ1, KCNQ1-KCNE1, and KCNQ1-KCNE3 currents in response to 3 s pulses to a range of voltages between −120 and +60 mV, with 10 s interpulse intervals, from a holding voltage of −80 mV, with a 1 s −30 mV tail pulse, as shown in voltage protocol (*upper left*). Channels were expressed by injection of corresponding cRNAs into *Xenopus laevis* oocytes and currents recorded 3 days postinjection by two-electrode voltage-clamp. Zero current levels indicated by dashed lines. *Adapted from Abbott GW. Biology of the KCNQ1 potassium channel.* New J Sci *2014;**2014**.*

recognized as a K^+ channel regulatory or β subunit. Three years later, we and others reported cloning of four other KCNE genes,[9,10] and the KCNE family is now recognized as a five-member class (in the human genome) of ion channel β subunits that exhibit ubiquitous expression, promiscuous and versatile activity, and multiple disease correlations. Each of the KCNE subunits has an extracellular N-terminus, an intracellular C-terminus, and a single transmembrane domain[11] (Fig. 1.1B).

THE MECHANISTIC BASIS FOR FUNCTION OF KCNE PROTEINS

KCNE proteins cannot generate current themselves, but they alter the behavior and facilitate the native functions of certain ion channels. Their primary partners are Kv channels. Each KCNE isoform is capable of regulating multiple Kv α subunits at least in vitro, and for some, we and others have established their promiscuity in vivo.[12] Not all Kv α subunits are known to be regulated by KCNEs, but several can be regulated by multiple KCNE isoforms. Therefore, there are many possible permutations of α-KCNE complexes, and these likely contribute greatly to the diversity of Kv currents in vivo.[13]

KCNE Regulation of KCNQ1 Channel Gating, Conductance, Ion Selectivity, and Pharmacology

The most commonly recognized modes of KCNE regulation of ion channels involve formation of complexes with altered channel activity at the plasma membrane compared to channels formed by the pore-forming subunits alone. This typically involves changes in the voltage dependence and/or kinetics of gating. The best known examples, and most diverse known functional outcomes, involve KCNQ1—which is differentially regulated by each of the five KCNE isoforms.[14] KCNE1 eliminates KCNQ1 inactivation,[15] increases its unitary conductance,[16] right-shifts its voltage dependence of activation, and—most noticeably—slows its activation five- to tenfold.[16,17] KCNQ1-KCNE1 complexes also have slightly altered ion selectivity compared to KCNQ1 homomers. The molecular mechanisms by which KCNE1 regulates the gating of KCNQ1 have been the subject of intense research efforts for many years and are still not fully resolved. The stoichiometry of KCNQ1 complexes has also long been debated and even to this day there is not full agreement. Evidence from toxin binding, dominant-negative mutagenesis, and fluorescence spectroscopy strongly suggests that 4:2 (KCNQ1:KCNE1) complexes exist[8,18,19] (Fig. 1.1B). However, some groups contend that 4:4 complexes can also exist, depending on subunit expression ratios.[20]

In terms of structure, the KCNE1 transmembrane domain (residues 45–71) adopts an α helical conformation with a slight curve. This curvature may allow the C-terminal, intracellular part of KCNE1 to interact with the S4-S5 linker region of KCNQ1 to slow channel activation, while permitting its extracellular N-terminal portion to sit in the cleft between the voltage sensor and pore domains of KCNQ1 near the extracellular face.[21] S4-S5 connects the voltage sensor to the activation gate and extensive mutagenesis, binding, and modeling studies support its interaction with the cytosolic domain of KCNE1.[22–24] Positioning of KCNE1 in this groove could stabilize the closed state in favor of the open state, resulting in the signature retardation of opening and also the right-shift in voltage dependence observed after KCNQ1-KCNE1 coassembly, although it is still debated whether KCNE1 slows voltage sensor movement or pore opening itself.[25–27]

Another compelling possibility fielded recently is that KCNQ1 channel voltage sensors exhibit an additional stable intermediate (not fully "activated") state that can nevertheless also open the pore, unlike the canonical *Shaker* Kv channel which is thought to require full voltage sensor activation before pore opening. It is contended that KCNE1, by altering the manner in which the KCNQ1 voltage sensor and pore interact, prevents formation of the intermediate state and also changes the conformation of the fully activated state, to achieve the array of effects it exerts on KCNQ1—including altered gating, permeation, and even pharmacology.[28]

KCNE2 effects are dramatically different. KCNQ1-KCNE2 channels are constitutively active,[29] probably resulting from left-shifted voltage dependence of activation and/or greatly slowed deactivation at a given voltage. In physiological conditions, this means that KCNQ1-KCNE2 conditions are much less voltage-dependent than KCNQ1 or KCNQ1-KCNE1 channels. As discussed later, this property permits KCNQ1-KCNE2 channels to serve a variety of essential functions in nonexcitable, polarized epithelial cells. This ability is facilitated by other facets endowed by KCNE2. For example, KCNQ1 channels are inhibited by low extracellular pH; in contrast, KCNE2 coassembly results in KCNQ1 current augmentation by extracellular low pH, an essential property of KCNQ1-KCNE2 channels in parietal cells, where they support activity of the gastric H^+/K^+-ATPase by recycling K^+ ion back into the stomach lumen. KCNQ1-KCNE2 macroscopic currents are relatively small compared to even homomeric KCNQ1,[29] and analysis of unitary conductances from all KCNQ1-based channels is technically very challenging because of a low, flickery conductance. Thus, our functional understanding of these important channels at the unitary level lags behind that of other, easier to study channels.

As with KCNE2, KCNQ1-KCNE3 channels are constitutively active,[30] the mechanism appearing to be primarily a strong left-shift in the voltage dependence of activation.[31,32] Work from mutagenesis studies in which KCNE1 transmembrane residues were swapped with those in equivalent

positions in KCNE3 strongly suggests that a portion of the KCNE3 transmembrane domain influences its ability to hold KCNQ1 open at rest.[33] In addition, we performed mutant cycle analysis and found that KCNE3 residues in the N-terminal domain that presumably lie near the extracellular side of the lipid bilayer interact with the KCNQ1 S4 helix of the voltage-sensing domain (VSD), helping to stabilize the activated conformation of the VSD.[34] The ability of KCNQ1-KCNE3 to open constitutively is probably essential to its function in the basolateral side of cells in the intestine, where it regulates cAMP-stimulated chloride secretion and also in the airway and mammary epithelia.[30]

KCNE4 and KCNE5 (also known as KCNE1L) are widely expressed but thus far relatively less studied than KCNE1, 2, and 3.[10,35–39] KCNE4 inhibits KCNQ1 function, possibly by right-shifting its voltage dependence of activation to the extent that KCNQ1 cannot be opened at voltages normally visited even under experimental conditions.[36,40] Likewise, KCNE5 is known to right-shift KCNQ1 voltage dependence of activation >140 mV more positive than that of homomeric KCNQ1.[38] Interestingly, KCNE4 and KCNE5 can each modulate KCNQ1-KCNE1 complexes, although the precise molecular mechanisms are uncertain and add further interest to the idea of stoichiometric flexibility and what we will refer to here as "subunit mosaicism" within KCNQ1-KCNEx (I_{Ks}) complexes.[37]

ROLES OF KCNE SUBUNITS IN CARDIAC ION CURRENTS AND ARRHYTHMOGENESIS

The most widely acknowledged role of the KCNE protein family is in the heart.[41] In human ventricular myocytes, two main Kv currents serve to repolarize the myocyte membranes to end each action potential.[42] hERG (for human ether-a-go-go related gene product) is the α subunit required for the primary repolarization current, I_{Kr} (rapidly activating K^+ current). KCNQ1 is the α subunit required to generate the slowly activating current, I_{Ks} (see previous discussion). I_{Ks}, like I_{Kr}, is also essential for human ventricular repolarization and appears to be particularly important when I_{Kr} is diminished, or during certain exercise activities including swimming.[43] Crucially, KCNE subunits modulate KCNQ1, hERG, and other important human cardiac Kv channel α subunits and are thought to be important for their correct function in the context of ventricular and/or atrial myocytes. We know this because inherited mutations in KCNE subunits cause similar ventricular or atrial arrhythmias to those observed in people with α subunit gene mutations (Table 1.1).

Cellular electrophysiology studies have shown how point mutations in KCNE genes can fundamentally alter the functional properties of heteromeric α-KCNE complexes, including the current density (for reasons

TABLE 1.1 Subset of *KCNE* Gene Variants Associated With Cardiac Arrhythmia for Which Cellular Electrophysiology Analyses Were Reported

Gene	Mutation	Disease	In Vitro Cellular Effects	References
KCNE1	A8V	LQT5, AF	I_{Ks} +9 mV positive shift in $V_{1/2}$ activation, no change in deactivation or activation time constants. I_{Kr} loss-of-function	44,45
KCNE1	G25V	Lone AF	I_{Ks} gain-of-function	46
KCNE1	R32H	LQT5	Gating not altered	45,47,48
KCNE1	38G versus 38S	AF, LQT5	I_{Ks} loss-of-function, reduced membrane $K_V7.1$ (KvLQT1) channel	49–53
KCNE1	V47F	LQT5	hERG gain-of-function	54
KCNE1	L51H	LQT5	Does not process properly, not found in membrane	54
KCNE1	G52R	LQT5	I_{Ks} reduced 50%	55
KCNE1	G60D	Lone AF	I_{Ks} gain-of-function, faster deactivation	46
KCNE1	S74L D76N	LQT5 (JLNS + RW)	D76N: I_{Ks}—smaller unitary currents and open probabilities Dominant negative I_{Kr}—loss-of-function S74L: I_{Ks} loss-of-function	56 57 16 54
KCNE1	Y81C	LQT5?	I_{Ks} loss-of-function, positive shift for voltage of activation	58
KCNE1	D85N	LQT5? DiLQTS DiTdP	No effect on I_{Ks}, $V_{1/2}$ of activation, or deactivation properties	59–67
KCNE1	W87R	LQT5	I_{Ks} loss-of-function, altered gating	54
KCNE1	R98W	LQT5?	Disrupts I_{Ks} trafficking, right-shifts voltage dependence of activation	68
KCNE1	V109I	LQT5	I_{Ks} loss-of-function (36%)	69
KCNE2	T8A Q9E	LQT6, diLQTS	Increases drug sensitivity of I_{Kr}	9,70
KCNE2	T10M	LQT6	I_{Kr} slow inactivation recovery and inactivation	71
KCNE2	M23L	AF	$I_{Q1\text{-}E2}$ and I_{Ks} gain-of-function	72
KCNE2	R27C	AF	$I_{Q1\text{-}E2}$ gain-of-function, $I_{Ca,L}$ suppression	73,74

TABLE 1.1 Subset of *KCNE* Gene Variants Associated With Cardiac Arrhythmia for Which Cellular Electrophysiology Analyses Were Reported —cont'd

Gene	Mutation	Disease	In Vitro Cellular Effects	References
KCNE2	M54T I57T A116V	LQT6, diLQTS, AF (I57T)	Pathological I_{Kr} loss-of-function ± drug. M54T and I57T also slow $K_V2.1$ activation; I57T increases $I_{Q1\text{-}E2}$ and I_{Ks} function	9,45,70,72
KCNE2	V65M	LQT6, Syncope	I_{Kr} loss-of-function, accelerated inactivation time course	75
KCNE3	T4A	LQTS? BrS	No effect on $I_{Q1\text{-}E3}$ I_{to} gain-of-function	76 77
KCNE3	R53H	AF	$I_{Q1\text{-}E3}$ gain-of-function	78
KCNE3	R99H	BrS LQTS?	$K_V4.3$, I_{to} gain-of-function $I_{Q1\text{-}E3}$ loss-of-function	79 76
KCNE4	E145D	AF	$I_{Q1\text{-}E4}$ gain-of-function	61
KCNE5	L65F	AF	I_{Ks} gain-of-function	80
KCNE5	Y81H D92E;E93X	BrS/ Idiopathic VF	$K_V4.3$ gain-of-function; No change in $I_{Q1\text{-}E5}$ density	81

AF, atrial fibrillation; *AV block*, atrioventricular block; *BrS*, Brugada syndrome; *diLQTS*, drug-induced long QT syndrome; *diTdP*, drug-induced torsade de pointes; *fs*, frame shift; *JLNS*, Jervell and Lange-Nielsen syndrome; *RWS*, Romano-Ward syndrome; *VF*, ventricular fibrillation. *Adapted from Crump SM, Abbott GW. Arrhythmogenic KCNE gene variants: current knowledge and future challenges.* Front Genet *2014;5:3; other sources include cited papers, http://www.genomed.org/lovd2/home.php, and http://www.fsm.it/cardmoc/.*

including trafficking defects and reduced unitary conductance) and the voltage dependence and kinetics of gating.[9,16,41] The perturbations disrupt electrical activity required for correct action potential duration and morphology leading to abnormal myocyte repolarization. What might appear a relatively innocuous event on a human body-surface ECG, eg, as lengthening of the QT interval, can serve as a substrate for reentrant arrhythmias that can rapidly degenerate into a condition termed *torsades de pointes*. This, in turn, can develop into ventricular fibrillation, a condition in which concerted, rhythmic contraction of the ventricles is replaced by chaotic smaller circuits that result in disorganized quivering of the heart rather than rhythmic pumping. This curtails the supply of essential oxygen via the bloodstream to important organs including the brain. This can result in loss of consciousness and sudden cardiac death; unless the individual is rapidly resuscitated using CPR and/or electrically defibrillated, there is little to no chance of recovery.[83,84] In contrast, atrial fibrillation (AF) is not generally acutely lethal but can increase the risk of life-threatening blood clots and stroke, and is the most common chronic arrhythmia, with an

estimated 2–3 million sufferers in the United States alone. As people age, there is a much greater likelihood of developing AF, with the majority of cases stemming from structural heart disease.[85] In addition, postoperative AF, which typically lasts a month, is a common side effect of cardiothoracic surgery.[86] However, some cases, referred to as "lone AF," occur in the absence of these predisposing factors; a subset of cases of lone AF have been attributed to mutations in ion channel genes, including *KCNE* genes (Table 1.1).

KCNE1 in Human and Mouse Heart

KCNQ1 was the first known partner for KCNEs and the large majority of the KCNE literature still revolves around regulation of KCNQ1. Whether this is historical bias or proportional to the importance of KCNQ1 in KCNE biology remains to be seen. The first-discovered, best-understood, and perhaps most important such complex in human heart is KCNQ1-KCNE1, which generates I_{Ks}. The uniquely slow-activating nature of I_{Ks} positions it to deliver a robust repolarizing force to end phase 3 of the ventricular action potential (Fig. 1.1). KCNE1 mutations, like those in KCNQ1, are most commonly associated with LQTS (for KCNE1 this is classified as LQT5) and rarely with AF (Table 1.1). LQTS-linked KCNE1 variants cause loss-of-function of KCNQ1-KCNE1 channels, either from misfolding/misprocessing, impaired trafficking to the surface, reduced unitary conductance, right-shifted voltage dependence of activation, or altered gating kinetics (Table 1.1). It is important to mention that native I_{Ks} complexes also contain several other proteins in addition to KCNQ1 and KCNE1, including Yotaio, calmodulin, PKA, 4D3, PP1, and AC9[87–89] (Fig. 1.2).

Particularly severe loss-of-function of KCNQ1-KCNE1 channels, such as that caused by a pathogenic mutation in both alleles for either gene, can cause the cardioauditory Jervell Lange-Nielsen syndrome, which comprises LQTS and bilateral sensorineural deafness.[90,91] This revelation uncovered another essential role of KCNQ1-KCNE1, that of K^+ secretion into the endolymph of the inner ear. While *KCNE1* mutations have taught us much about the obligate role of KCNE subunits in vivo, it is important to remember that only around 1% of sequenced LQTS cases arise from *KCNE1* variants (compare with >40% each for HERG and KCNQ1), and the other *KCNE* genes (especially *KCNE3-5*) are probably even rarer causes of LQTS. However, *KCNE* coding regions, including that of *KCNE1*, are comparatively small (~400 bases) meaning that the probability of mutations arising in them is proportionately lower than in much larger channel α subunit genes.[41] Even if one includes both introns and exons, *KCNE2*, for example, is per base of more pathophysiological significance that the *SCN5A* sodium channel gene that accounts for about 10% of LQTS cases.

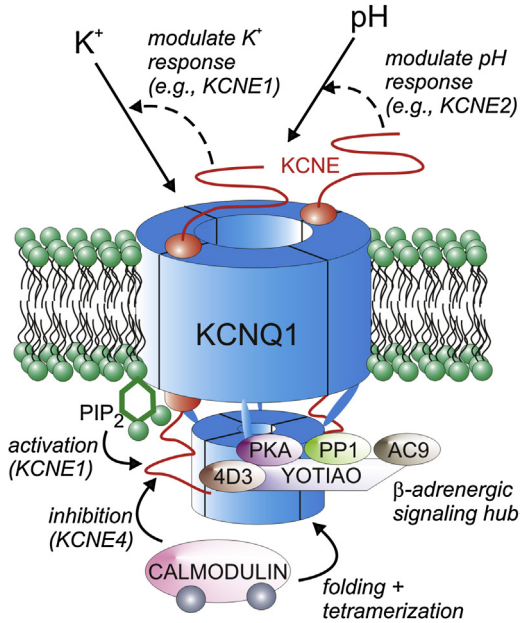

FIGURE 1.2 I_{Ks} **complexes comprise multiple subunit types.** Schematic of the various KCNE and non-KCNQ subunits that regulate KCNQ1 and their crosstalk. *PDE4D3*, phosphodiesterase 4D3; *AC9*, adenylyl cyclase 9; *PIP_2*, phosphatidylinositol 4,5-bisphosphate; *PKA*, protein kinase A; *PP1*, protein phosphatase 1. *Adapted from Abbott GW. Biology of the KCNQ1 potassium channel*. New J Sci *2014;**2014***.

Human KCNE1 variants are associated with lone AF; most notably, the ratio of KCNE1-38G versus 38S polymorphisms an individual harbors appears to influence AF predisposition.[49,92] AF is thought to be caused by shortening of the atrial effective refractory period, and therefore gain-of-function mutations in KCNQ1, and the KCNE subunits that regulate it, are typically observed in the rare cases when AF can be linked to a specific gene variant. We previously discovered, using transcriptomics, that open chest surgeries associated with postoperative AF remodel a number of atrial genes in pigs, most strikingly *KCNE1*. This finding was subsequently mirrored in a human study, in which the *KCNE1* 112G>A polymorphism was linked to increased susceptibility to postoperative AF.[93]

Aside from regulation of KCNQ1, KCNE1 also modulates hERG, the other major repolarizing Kv channel in human ventricles. KCNE1 doubles hERG currents upon their heterologous coexpression in mammalian cell lines,[94] and *KCNE1* mutations impair native hERG currents in isolated myocytes.[54] The mechanism for KCNE1 augmentation of hERG is unknown, as is the relative contribution of KCNE1 to KCNQ1 versus hERG channels in native cardiac myocytes. It is interesting to note that KCNQ1 may form complexes with hERG channels in the heart, suggesting

that KCNE1 regulation of either subunit, and effects of *KCNE1* mutations on channel function, may be even more complex than first suspected.[95,96]

KCNE2-5 in Human Heart

KCNE2 and KCNE3 each dramatically alter the voltage dependence of KCNQ1 gating such that KCNQ1-KCNE2 and KCNQ1-KCNE3 channels are constitutively active, forming K^+-selective leak channels at resting membrane potentials[29,30] (Fig. 1.1C). In the heart, the role of these complexes is unclear, with suggestions that KCNE2 and KCNE3 might contribute to regulation of KCNQ1-KCNE1[97–99]; such mixed-KCNE complexes likely do not have constitutive activation. KCNE2 and KCNE3 are important in human and mouse heart physiology, however, via different mechanisms.

Human *KCNE2* gene variants are associated with inherited and drug-induced ventricular arrhythmias. We discovered that KCNE2 regulates the hERG K^+ channel, modifying its unitary conductance, gating kinetics, and pharmacology.[9] KCNE2 gene variants, including both rare mutations and more common polymorphisms, are deleterious to hERG-KCNE2 channel function; those associated with LQTS reduce hERG-KCNE2 current density and/or increase sensitivity to drug block, by various mechanisms.[9] One of the more interesting sequence variant effects is that of KCNE2-T8A. This variant is absent in African Americans but present in >1% of Caucasian Americans. hERG-KCNE2-T8A channels function normally at baseline but are more susceptible to blockade by the sulfamethoxazole component of the antibiotic Bactrim.[70] This increased sensitivity was discovered to arise from loss of a glycosylation site in KCNE2 that, when intact, presumably partially shields hERG-KCNE2 channels from block by sulfamethoxazole.[100]

The pathogenic cardiac effects of KCNE2 mutations may be even more complex, however, because KCNE2 can regulate a number of other cardiac ion channels and arrhythmogenic KCNE2 mutations have been shown to alter the function of some of these complexes as well. Thus, KCNE2 modulates Kv1.5, Kv2.1, Kv4.2, and Kv4.3,[101–103] monovalent cation nonspecific HCN pacemaker channels,[104,105] and even reportedly the cardiac L-type calcium channel, Cav1.2.[73] This suggests a master regulatory role for KCNE2 in the heart and therefore the potential for a multifaceted arrhythmia syndrome when KCNE2 malfunctions (and see Ref. 106). KCNE2 mutations R27C, M23L, and I57T have each been associated with lone AF; these variants exert gain-of-function effects on KCNQ1 (and KCNQ1-KCNE1) (Table 1.1); in addition, R27C increases the suppressive action of KCNE2 on Cav1.2.[73] Either of these effects could contribute to atrial myocyte action potential shortening, a substrate for AF.