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KCNE1 and KCNE3: the yin and yang of voltage-gated K^+ channel regulation

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Abstract

The human KCNE gene family comprises five genes encoding single transmembrane-spanning ion channel regulatory subunits. The primary function of KCNE genes appears to be regulation of voltage-gated potassium (Kv) channels, and the best-understood KCNE complexes are with the KCNQ1 Kv α subunit. Here, we review the often opposite effects of KCNE1 and KCNE3 on Kv channel biology, with an emphasis on regulation of KCNQ1. Slow-activating I_{Ks} channel complexes formed by KCNQ1 and KCNE1 are essential for human ventricular myocyte repolarization, while constitutively active KCNQ1-KCNE3 channels are important in the intestine. Inherited sequence variants in human KCNE1 and KCNE3 cause cardiac arrhythmias but by different mechanisms, and each is important for hearing in unique ways. Because of their contrasting effects on KCNQ1 function, KCNE1 and KCNE3 have proved an invaluable tool in the mechanistic understanding of how channel gating can be manipulated, and each may also provide a window into novel insights and new therapeutic opportunities in K^+ channel pharmacology. Finally, findings from studies of *Kcne1*$^{-/-}$ and *Kcne3*$^{-/-}$ mouse lines serve to illustrate the complexity of KCNE biology and KCNE-linked disease states.

Graphical abstract

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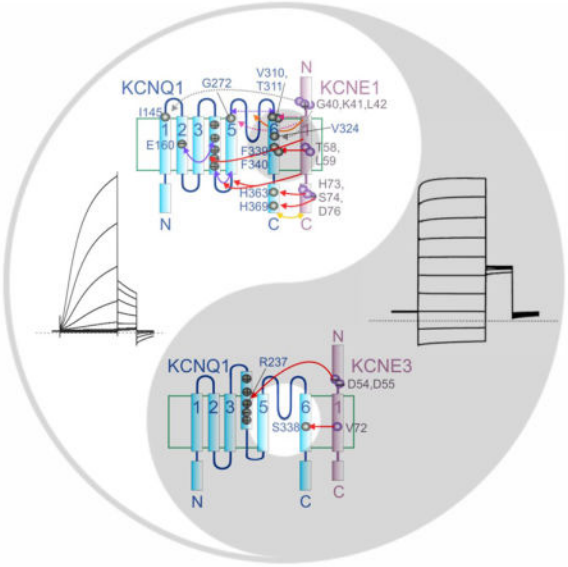

Keywords

auditory; cardiac arrhythmia; intestine; inherited deafness; Long QT syndrome; potassium channel; voltage-gated

Introduction

Bioelectricity - the electrical activity generated by living organisms - is observable across all six kingdoms of life, and essential in higher animals for processes including fertilization, neuronal firing, and muscular contraction. Electrical signals are conducted primarily by ion channels, which have evolved the capability to selectively and rapidly conduct charged, aqueous ions across the hydrophobic barrier established by the plasma membrane.

Within the ion channels, the S4 superfamily contains those that respond to changes in membrane potential via a voltage sensor that includes the S4 domain. The S4 is so named because it is the fourth transmembrane (TM) segment in the 6-TM module that constitutes the pore-forming (α) subunit of eukaryotic voltage-gated potassium (Kv) channels and some prokaryotic voltage-gated sodium (Nav) and calcium (Cav) channels[1]. While each of these voltage-gated channel classes achieve their respective ion selectivity by distinct mechanisms, the atomic structure and signature sequence for K^+ selectivity is highly conserved between primitive tetrameric bacterial K^+ channels lacking a voltage sensor[2], tetrameric mammalian Kv channels carrying the S4[3], and even dimeric “two-pore” K2P channels such as human K2P1[4]. Mammalian Nav and Cav channel α subunits consist of four repeats of the 6-TM module whereas mammalian Kv channels form as a tetramer of four non-covalently bound 6-TM α subunits (Figure 1A).

In Kvs, Navs and Cavs, the voltage sensor is attached to the channel “gate” and when the voltage sensor senses a change in membrane potential and moves in response to this, the movement is communicated to the gate to open or close the pore depending on the channel

type; all three channel types are opened by membrane depolarization[1]. Hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels are activated (opened) by membrane hyperpolarization; these channels pass both Na^+ and K^+ and are referred to as pacemaker channels because they trigger subsequent action potentials in response to undershoot from the previous action potential, and are essential for controlling the heart beat and some rhythmic neuronal firing[5].

Of all the known Kv channel α subunits, only one, KCNQ1, has thus far been discovered to have the ability to ostensibly lose its voltage dependence. KCNQ1 co-assembles with members of the KCNE family of single transmembrane segment K^+ ion channel ancillary or β subunits (Figure 1A–C) to enable it to juggle such contrasting roles as cardiac myocyte repolarization, and epithelial cell ion homeostasis/transporter regulation[6]. KCNQ1 exists as a tetramer of α subunits in complexes with two KCNE1 subunits at the plasma membrane[7–9], although stoichiometric variability (between 4:2 and 4:4, α:β) has also been proposed [10,11] (Figure 1B). The stoichiometry of other Kv-KCNE complexes other than KCNQ1-KCNE1 has not been reported. Channels formed by KCNQ1 and KCNE1 - originally named slowly activating K^+ current (IsK)[12] and also referred to as Minimal K^+ channel (MinK) [13] - open very slowly, and less easily at negative voltages than homomeric KCNQ1 channels[14,15] (Figure 2). In sharp contrast, KCNE3 (originally named MinK-related peptide 2, MiRP2) [16] has even more striking effects, locking open the KCNQ1 S4 to almost entirely remove the voltage dependence of KCNQ1 activation, converting it to a K^+ leak channel[17,18]. This review covers the mechanisms and physiological roles of KCNE1 and KCNE3 regulation of KCNQ1 and other Kv channels. A recent companion review was focused on KCNE2[19].

KCNE1 and KCNE3 in the context of the KCNE gene family

The first-recognized member of the KCNE family, KCNE1 was discovered by expression cloning via injection of rat kidney mRNA into *Xenopus laevis* oocytes. One fraction of RNA generated a slowly activating, K^+-selective and voltage-dependent current measurable by two-electrode voltage-clamp (TEVC) electrophysiology[12]. This finding initially caused confusion because the sequenced KCNE1 protein was much smaller than, and bore no sequence similarity to, the known Kv α subunits[20,21]. The current generated by KCNE1 strongly resembled the mammalian cardiac Kv current known as I_{Ks} (slow-activating K^+ current). Eight years after KCNE1 was cloned, KCNQ1 (then named KvLQT1, also referred to as Kv7.1) was positionally cloned via its linkage to inherited Long QT syndrome (LQTS), a defect in ventricular repolarization that can result from mutations in KCNQ1[22]. KCNQ1 was found, like KCNE1, to be expressed in human heart. Furthermore, *Xenopus laevis* KCNQ1 was found to be endogenously expressed in *Xenopus* oocytes. Co-expression of KCNQ1 and KCNE1 recapitulated the characteristics of I_{Ks} in cells that, unlike *Xenopus* oocytes, do not express sufficient endogenous KCNQ1 to yield currents upon heterologous expression of KCNQ1 alone, i.e., Chinese Hamster ovary (CHO) cells. KCNE1 was thus recast as a regulatory, or β, subunit of KCNQ1[14,15], and was swiftly discovered, like KCNQ1, to associate with LQTS[23,24].

KCNE1 was a white elephant for a decade, until the discovery of its relatives using Basic Local Alignment Search Tool (BLAST) screening of online libraries of expressed sequence tags (ESTs)[16]. Although the five *KCNE* genes share relatively little similarity with one another, they each exhibit 1-TM topology with an extracellular N-terminal domain and intracellular C-terminal domain. In addition, each possesses a consensus protein kinase C (PKC) phosphorylation site in the membrane-proximal portion of the cytoplasmic C-terminal region[19]. BLAST searching with features of KCNE1 known to be important for its function circumvented the difficulties presented by relatively low family-wide sequence identity, and uncovered KCNE2, 3 and 4 – which we initially termed MinK-related peptides (MiRPs) 1, 2 and 3[16]. A fifth member, KCNE1L or KCNE5, was also discovered[25].

KCNE1 and KCNE3 regulation of KCNQ1

KCNQ1 is a highly versatile Kv α subunit, which is regulated by a number of different types of protein to produce functionally distinct channel complexes[6]. All five of the KCNE proteins regulate KCNQ1 with distinct functional outcomes, and the effects of KCNE1 and KCNE3 are particularly striking. When heterologously co-expressed with KCNQ1 in mammalian cell lines such as Chinese Hamster ovary (CHO) or human embryonic kidney (HEK) cells, KCNE1 right-shifts the voltage dependence of KCNQ1 activation (opening), slows its activation 5–10 fold[14,15], increases its unitary conductance 4-fold (as measured by noise variance analysis)[26], slows its deactivation (closing) and eliminates its inactivation[27]. In sum, this increases KCNQ1 peak currents at positive voltages several-fold (Figure 2).

In contrast, KCNE3 holds open KCNQ1 such that the complex is constitutively active, no longer relying on membrane depolarization to open[17]. Instead, current magnitude (and direction) through KCNQ1-KCNE3 is dictated almost exclusively by driving force (Figure 2). Direct structural studies of the KCNE proteins in isolation (not complexed with α subunits) revealed that the TM segment of KCNE1 is α-helical, and that approximately half the KCNE1 extracellular domain adopts an α helical conformation[28–31]. Despite relatively low sequence similarity with KCNE1, the secondary structure distributions of the KCNE3 TM and extracellular domains are quite similar to those of KCNE1 [32]. A plethora of structure-function studies have been directed toward understanding the molecular bases for these differences, with The McDonald lab discovered a single residue in the TM region (T58 in KCNE1; V72 in KCNE3) that when switched between KCNE1 and KCNE3 could swap their activation properties. Thus, V72T-KCNE3 slows KCNQ1 activation almost as much as KCNE1 does, and eliminates KCNQ1-KCNE3 constitutive activation[33]. Conversely, T58V KCNE1 introduces half as much constitutive current as observed for KCNQ1-KCNE3, and increases the KCNQ1-KCNE1 activation rate 3-fold. Furthermore, concomitant introduction of two KCNE3 residues, to yield F57T, T58V-KCNE1, yielded KCNQ1-KCNE1 channels that were only twofold slower activating than KCNQ1-KCNE3 and almost matched its fractional constitutive current; these channels could be closed by holding for 3 s at −120 mV instead of the normal −80 mV[33].

We subsequently found, using tryptophan tolerance scanning of KCNQ1 S6 followed by mutagenesis of the KCNE1 and KCNE3 residues identified by the McDonald lab, that KCNE1 T58 and L59 interact with KCNQ1 F339 and F340, whereas KCNE3 V72 interacts

with KCNQ1 S338[34]; of note, T58 and L59 mutants were among the first described in KCNE1-linked Jervell and Lange-Nielsen syndrome (JLNS), a cardioauditory syndrome comprising LQTS and sensorineural deafness[13] (see below). It should be noted that the McDonald lab study utilized the CHO cell expression system[33] whereas our study involved *Xenopus* oocytes. An interesting phenomenon of KCNQ1-KCNE3 channels is that they exhibit an almost perfectly linear current-voltage relationship when expressed in *Xenopus laevis* oocytes, while in the typical mammalian heterologous expression systems they exhibit some constitutive activation but a much less linear IV curve. The basis for this difference, be it an artifact of the different techniques used to record whole-cell currents in oocytes (two-electrode voltage clamp, TEVC) versus mammalian cells (patch clamp), or a difference in co-factor expression between the systems, has not to the author's knowledge been reported. While one may assume the mammalian cells are a truer representation of what might occur *in vivo* in mammalian tissues, the oocyte system more dramatically highlights the capabilities of KCNE3.

Other KCNE1 and KCNE3 residues are also important for maintaining their tight control of KCNQ1 activation, as uncovered in oocyte studies using TEVC. In KCNE1, the C-terminal domain appears to exert a strong influence on KCNQ1 activation, regulating channel assembly, destabilizing the KCNQ1 open state, altering deactivation rate and modulating rate-dependent facilitation of KCNQ1 activity[35]. The intracellular end of the KCNE1 transmembrane region is proposed to sit on the S5 end of the KCNQ1 S4-S5 linker (a portion of the channel that links the gate to the voltage sensor)[30], and protein-protein interactions were detected between cysteines substituted for wild-type resides H363 (in the S6-proximal region of the KCNQ1 C-terminal domain) and H73, S74 and D76 in the KCNE1 C-terminal domain, and between residues H369 with D76[36] (Figure 3A). These interactions probably contribute strongly to slowing KCNQ1 activation and, notably, human KCNE1 S74L and D76N mutations are among the first-described, most-studied, and most pathogenic KCNE1 variants[14]. The membrane-proximal portion of the extracellular domain of KCNE1 (residues G40 in the activated state and K41 in the resting state) comes close to KCNQ1 S1 (I145, at the extracellular end), as evidenced from substituted cysteine disulfide trapping. Similarly, a cysteine substituted at KCNE1 L42 can be linked to V324C in KCNQ1 S6, with the result of eliminating deactivation. These interactions themselves might not necessarily be highly influential in the gating of wild-type KCNQ1-KCNE1 complexes but they suggest how KCNE1 orientation might change with respect to KCNQ1 during gating[37,38] (Figure 3A).

In contrast, in KCNE3, the transmembrane domain appears to override the influence of its C-terminal domain[39]. In addition, The KCNE3 N-terminal region possesses two acidic residues crucial for the robust constitutive current exhibited by KCNQ1-KCNE3 channels when expressed in oocytes. Using double-mutant thermodynamic cycle analysis, we discovered energetic coupling of KCNE3 residues D54 and D55 specifically to residue R237 in the voltage-sensing S4 helix of KCNQ1[40]. We had previously found that the relative charge paucity of KCNQ1 S4 (+3, the lowest of all known eukaryotic voltage-dependent ion channels) was instrumental in the functional flexibility of KCNQ1 in terms of regulation by KCNE subunits[18]. Neutralization of R231 within KCNQ1 S4, by replacement with alanine, converts KCNQ1 to a K^+ leak channel in the absence of KCNEs, and the same is achieved in

related α subunit KCNQ4 by a triple mutation that mimics the charge balance of R231A-KCNQ1[18,41]. Homomeric R237A-KCNQ1 channels exhibit slightly right-shifted activation voltage dependence compared to homomeric KCNQ1, but the former accumulate in the open state with repetitive membrane depolarizations, deactivating very slowly upon repolarization[18]. In KCNQ1-KCNE3 complexes, KCNQ1-R237 appears to engage in electrostatic interactions with KCNE3 D54 and D55 to help stabilize the KCNQ1 S4, and therefore also the pore, in the activated state, even at negative voltages (deactivation can be seen to occur over several seconds when hyperpolarizing to −120 mV) (Figure 3A). Interestingly, KCNE3 D54 partially protects KCNQ1-KCNE3 channels from the inhibitory effects of loss of plasma membrane phospholipid head groups. Normally, these negatively charged phosphocholines stabilize the activated conformation of S4, facilitating voltage-dependent activation. Removal of these head groups via hydrolysis by, for example, sphingomyelinase C, inhibits activity of channels including Kv2.1[42] and KCNQ1, but KCNE3 (and not KCNE1) helps maintain KCNQ1 activity in the face of sphingomyelinase C because KCNE3-D54 mimics the S4-stabilizing action of membrane phosphocholines[40].

As striking as the constitutive activation of KCNQ1 endowed by KCNE3, is the laboriously slow activation endowed by KCNE1. As covered above, the KCNE1 C-terminal domain and to some extent the transmembrane domain may be important in slowing KCNQ1 activation, but is this achieved by slowing the voltage sensor, the pore opening, or both? There are at least two camps in terms of this aspect of the mechanistic underpinnings of slow KCNQ1-KCNE1 activation. The Goldstein and Bezanilla labs approached the problem using cut-open oocyte recording, a technique that permits much better voltage clamp and improved time resolution compared to conventional TEVC, facilitating measurement of gating currents – the current generated from movement of the charged voltage sensor itself. The cut-open oocyte recordings were combined with site-directed fluorimetry to also monitor voltage sensor movement by a complementary approach. They discovered that unlike homomeric KCNQ1, during KCNQ1-KCNE1 activation S4 moves too slowly to permit resolution of the gating current; by fluorimetry S4 was found to move 30-fold slower than that of the oft-studied Shaker Kv channel[43].

Nakajo and Kubo found, using methanethiosulfonate (MTS) modification of cysteine-substituted KCNQ1 residues, that accessibility of A226C-KCNQ1, a substituted residue near the extracellular side of KCNQ1 S4, was 13-fold slower when KCNE1 was co-expressed compared to KCNQ1 alone. In contrast, when KCNE3 was co-expressed, KCNQ1 A226C accessibility was voltage-independent. This is consistent with the slow S4 movement model for KCNQ1-KCNE1 activation, although it is also consistent with S4 equilibrium rather than speed of movement being modulated by KCNE1[44]. Subsequent work by Nakajo and Kubo also suggested KCNE1 modulates interactions between S4 and S5 to affect activation gating, which could affect S4 movement speed and/or coupling of S4 to the channel gate[45]. The Seebohm lab found that KCNE1 interacts with both S4 and S5/S6 to form what is probably a stable pre-open state that may slow activation[46]. Utilizing voltage clamp fluorimetry of *Xenopus* oocyte-expressed channels, the Kass lab formulated a dual-effect model for KCNE1 regulation of KCNQ1, in which KCNQ1 can open after activation of just one S4, while KCNQ1-KCNE1 needs all four S4s to shift before the pore opens. This model incorporates both slow S4 movement, and the need for all four S4s to open, as the basis of

slow KCNQ1-KCNE1 activation[47,48]. The Fedida lab found using single channel analysis that KCNQ1-KCNE1 flits between a variety of subconductance states, behavior that may or may not also exist in faster channels but could be too rapid to resolve in these cases, and may strongly influence opening and closing rates of KCNQ1-KCNE1[49].

The jury is clearly still out over the specifics, but in general terms it appears KCNE1 interaction with S4 retards KCNQ1-KCNE1 activation, directly and/or or via altered interaction with S4 and S5/S6. Discrepancies between different studies could arise from different preparations, protocols and interpretations. Interaction of KCNE1 with KCNQ1 S4 may also generate the right-shift in voltage dependence of activation induced by KCNE1, possibly by altering the manner in which S4 senses the stabilizing acidic residues in other, nearby KCNQ1 TM domains[46,50,51].

Low mobility of the KCNE1-bound KCNQ1 S4 was also recently suggested to underlie the slow deactivation conferred by KCNE1[52]. In this comprehensive combination of experimental work, and modeling using elastic network analysis, loss of KCNQ1 C-type (slow) inactivation, another change conferred by KCNE1 co-assembly, was assessed in the context of acidic residues that influence slow inactivation of KcsA (the *Steptomyces lividans* K^+ channel used by the McKinnon lab to produce the first high-resolution K^+ channel structure[2]). It was suggested that KCNE1 limits positional fluctuations in the KCNQ1 outer vestibule and selectivity filter that drive slow inactivation, thereby eliminating or at least dampening the inactivation process. Finally, the increased conduction of KCNQ1 upon KCNE1 co-assembly was attributed in this study to a shift in KCNQ1 residues G272, V310 and T311 such that they move in concert with an entire “dynamic domain” in the pore. This is proposed to increase the scale of pore movement and therefore increase conductance, and is consistent with the results of previous mutagenesis studies[52]. The contrasting mechanisms by which KCNE1 and KCNE3 exert their effects on KCNQ1 gating and conductance, and possible locations of KCNE1 and KCNE3 within complexes with KCNQ1, are summarized in Figure 3A and B.

In addition, KCNE1 modulates KCNQ1 internalization from the plasma membrane. While KCNQ1 channels can be internalized by Nedd4/Nedd4-like- and Rab5-dependent processes with or without KCNE1 co-assembly[53,54], KCNE1 mediates an alternative process, clathrin-mediated endocytosis of KCNQ1[55]. This dynamin-dependent process is enhanced by PKC phosphorylation of KCNE1 at residue S103[56], explaining previous findings that S102 phosphorylation diminished currents generated by KCNE1 (in complex with endogenous KCNQ1) in *Xenopus* oocytes[57,58].

KCNE1 and KCNE3 also exhibit contrasting effects on the functional outcomes of KCNQ1 regulation by other factors. Serine 27 in the KCNQ1 N-terminal region can be phosphorylated by protein kinase A (PKA), a physiologically important mechanism for β-adrenergic stimulation of cardiac I_{Ks}. Although S27 can be phosphorylated regardless of the co-expressed KCNE isoform, the functional effect also requires KCNE1 (or KCNE2) and the cytoplasmic protein yotiao in the complex, despite the PKA site being on KCNQ1 itself. KCNQ1-KCNE3 complexes do not show the same upregulation in response to PKA phosphorylation of KCNQ1 S27[59]. Of note, KCNE1 increases the sensitivity of KCNQ1

channels to phosphatidylinositol 4,5-bisphosphate (PIP_2), a plasma membrane lipid that acts as a co-factor for a variety of ion channels and augments I_{Ks}. It is not yet known whether KCNE3 has similar effects, but all members of the KCNE family possess similar residues to those important for modifying the manner in which PIP_2 interacts with KCNQ1[60].

KCNE1 and KCNE3 regulation of other Kv α subunits

Although KCNE1 and KCNE3 regulation of other Kv channels is not generally as well understood as their effects on KCNQ1, it is interesting to note that their regulation of other α subunits also typically results in disparate outcomes (Table 1). The first non-KCNQ1 α subunit found to be regulated by KCNE1 was the human ether-a-go-go related gene product (hERG, also termed Kv11.1 or KCNH2), the channel primarily responsible for driving human ventricular repolarization, especially at resting heart rates. KCNE1 increases hERG current density by a still unresolved mechanism in heterologous expression studies[61], and probably regulates hERG in the heart[62–64]. In contrast, KCNE3 strongly inhibits hERG, again by an unresolved mechanism[17], although the same KCNE3 substitution (R83H) that disrupts ability to constitutively open KCNQ1 channels and augment Kv3.4 currents[65] also blunts the ability of KCNE3 to inhibit hERG[66]. Interestingly, KCNE1 and KCNE3 are reported to form tripartite complexes with Kv12.2 (also termed ELK2 or KCNH3), inhibiting its surface expression and activation in *Xenopus* oocytes; this may also occur in mouse brain[67].

KCNE1 and KCNE3 both slow Kv2.1 activation and deactivation, possibly increasing the diversity of Kv2.1 currents in heart and brain[64,68], and one of the rare instances in which these two KCNEs exhibit comparable effects on the activity of a specific Kv channel. In contrast, KCNE1 and KCNE3 have opposite effects on Kv3.4, a rapidly inactivating, N-type α subunit important in skeletal muscle and the CNS – albeit by different mechanisms. KCNE1 robustly inhibits Kv3.4 activity by retaining it early in the secretory pathway (endoplasmic reticulum and/or Golgi apparatus). We discovered that this provides a mechanism by which cells can ensure only mixed N-type/delayed rectifier channel complexes with intermediate inactivation kinetics, and not homomeric N-type α subunit channels, reach the plasma membrane. Both KCNE1 and KCNE2 exhibit this retention ability, and they can retain all three classic N-type, inactivation domain-containing Kv α subunits (Kv1.4, Kv3.3 and Kv3.4) until rescue by same-subfamily delayed rectifiers[69,70]. Conversely, KCNE3 augments activity of Kv3.4 channels, by a mechanism involving left-shifted voltage dependence of activation, increased unitary conductance, accelerated recovery from inactivation, and suppression of cumulative inactivation[65]. With respect to regulation of Kv3.1, Kv3.2, and Kv3.1-Kv3.2 heteromers, KCNE1 and KCNE3 both slow activation and deactivation and accelerate inactivation, but the effects of KCNE1 are of much greater magnitude[71].

KCNE3 was recently found to inhibit Kv4.2, and Kv4.2-KCNE3 complexes may contribute to spike frequency and other properties in auditory neurons[72] (see below), while no effects were observed for KCNE1 with Kv4.2 in *Xenopus* oocyte co-expression studies (albeit using a staggered, α subunit-first, cRNA injection protocol)[73]. Further, KCNE3 was found to inhibit Kv4.3 (fourfold reduction in current density) in CHO cells[74], while in contrast, in

HEK cells KCNE1 augmented Kv4.3 current density fivefold and slowed its inactivation [75]. Association of the cytosolic ancillary subunit, KChIP2, altered these effects. Thus, in tripartite complexes, all KCNEs accelerated activation and inactivation of Kv4.3-KChIP2 channel complexes, although compared to complexes formed with KCNE1, Kv4.3-KChIP2-KCNE3 channels exhibited lower current density, and slightly more negative half-maximal voltage dependence of steady-state activation and inactivation[76]. One or more of the KCNE subunits may thus contribute to functional diversity of cardiac I_{to}.

Returning to the KCNQ family, in both *Xenopus* oocytes and HEK cells, KCNE1 reportedly slows the activation of KCNQ5, decreases its inward rectification at highly depolarized voltages, and increases its peak current; conversely, KCNE3 inhibits KCNQ5[77]. Similarly, KCNE1 appears to mildly augment KCNQ4 current when co-expressed in *Xenopus* oocytes, whereas KCNE3 strongly inhibits KCNQ4 in this expression system[17,78].

KCNE1, KCNE2 and KCNE3 show sex-dependent differences in expression that arise from hormonal influence and determine some sex-specific aspects of mammalian physiology. Cardiac KCNE2 expression is upregulated by estrogen via a direct genomic mechanism[79]. KCNE1 and KCNE3 (but not KCNE2) are expressed in rat colonic crypts and highly enriched in male versus female rodents; during the estrus cycle, colonic expression of KCNE3 (and colonic partner KCNQ1) fluctuates in a manner consistent with KCNE3 downregulation by estrogen, via PKC phosphorylation of KCNE3 serine 82. In heterologous expression experiments, estrogen inhibited KCNQ1-KCNE3 activity, but not that of KCNQ1-KCNE1[80–82].

In contrast, KCNE1, 3 and 5 expression is upregulated in concert with that of the orphan nuclear receptor, estrogen-related receptor γ (ERRγ), in human syncytiotrophoblasts, and is downregulated by hypoxia; KCNE4 displays the reverse pattern. KCNE1 and KCNE3 expression in trophoblast cells is downregulated by shRNA suppression of ERRγ and KCNE1 contains a putative ERRγ response element within its 5′ flanking region[83]. KCNE1 and KCNE2 expression was also found to be downregulated in ERRγ null mouse hearts, a similar effect was observed for KCNE2 in parietal cells, and KCNE2 (like KCNE1) was found to contain a ERRγ responsive element that binds ERRγ[84].

Physiological roles for KCNE1: the heart and inner ear

The best-understood physiological roles for KCNE1 are encapsulated by JLNS, an inherited cardioauditory syndrome that results from severe disruption of KCNQ1-KCNE1 channels such as occurs with biallelic mutations in human *KCNE1* or *KCNQ1*[23,85]. The cardiac element of JLNS is LQTS, caused by loss of function of ventricular KCNQ1-KCNE1 channels, eroding the repolarization reserve of ventricular myocytes and delaying ventricular repolarization. Thus, the slow- and relatively positive membrane potential-activating KCNQ1-KCNE1 channel, which generates I_{Ks}, is important for repolarizing human ventricular myocytes to end their action potential in readiness for the next heartbeat[24,86]. I_{Ks} appears to be most important during physical exertion or other contexts when β–adrenergic stimulation increases I_{Ks} density to compensate for higher heart rates. At other times, I_{Kr}

(generated by hERG, which is regulated *in vivo* by KCNE1 and KCNE2) is probably dominant in human ventricles[87,88].

KCNE1 mutants more commonly cause the LQT5 form of LQTS, without overt auditory symptoms, and presumably though disruption of I_{Ks} complex function, although these mutants can also cause loss-of-function of hERG-KCNE1 channels and therefore potentially ventricular I_{Kr} *in vivo*[89]. To the author's knowledge, *KCNE1* sequence variation has not be linked to Brugada syndrome or to Short QT syndrome (SQTS), either of which (opposite to LQTS) can result from gain of function in ventricular Kv channels[90,91]. However, a *KCNQ1* mutation was recently discovered that appears to shorten the QT interval by impairing association of KCNQ1 with KCNE1, leading to accelerated activation and a negative shift in the voltage dependence of activation of I_{Ks}; the mutation also decreased inactivation of homomeric KCNQ1[92]. Human *KCNE1* sequence variants in its extracellular portion are associated with the relatively rare, idiopathic form of atrial fibrillation (AF), with the underlying mechanism considered to be gain of function of atrial myocyte KCNQ1-KCNE1 channels. In addition, a more common KCNE1 polymorphism, S38G, has been linked to altered predisposition to AF and LQTS, with environmental and other genetic factors influencing this predisposition[93–96]. The same polymorphism influences predisposition to postoperative atrial fibrillation[97], a prevalent arrhythmia following cardiothoracic surgery, and KCNE1 is downregulated in the atria of pigs following lung lobectomy[98]. Human *KCNE1* sequence variants associated with human disease are summarized in Table 2.

While KCNQ1-KCNE1 channels activate much faster at body temperature than the classic slow activation they exhibit at room temperature[99] - which makes the effects of KCNE1 particularly apparent - KCNE1 induces other changes in KCNQ1 important for their function together in the heart. As explained above, KCNE1 (together with a raft of cytosolic regulatory proteins) facilitates PKA upregulation of I_{Ks} in response to β adrenergic stimulation[100–105]. KCNE1 also appears to prime KCNQ1 to be ready to respond to the need for elevated heart rate by inducing a reserve of near-open closed states prepared for rapid activation when needed[87], such that I_{Ks} complexes can be thought of as the ventricles' 'minutemen'. As explained earlier, KCNE1 mediates PKC-stimulated endocytosis of KCNQ1-KCNE1 channels, providing an alternate pathway for downregulation of I_{Ks} (and also perhaps a therapeutic window for counteracting QT prolongation, if this process can be disrupted)[56]. Finally, elimination of KCNQ1 slow inactivation by KCNE1 may also better enable I_{Ks} to sustain rapid heart rates without current diminishment.

The non-inactivating status endowed by KCNE1 may also facilitate the established function of KCNQ1-KCNE1 in the inner ear. Although KCNQ1-KCNE1 channels activate voltage-dependently, they are capable of sustained activity at the membrane potentials typical for the apical membrane of strial marginal cells and dark cells of the inner ear (0 to +10 mV). KCNQ1-KCNE1 provides a conduit for K^+ secretion, thus recycling K^+ in the endolymph of the inner ear. In the human ear, loss of this recycling is sufficient to cause bilateral sensorineural deafness; *Kcnq1* deletion in mice revealed that this is associated with morphological abnormalities because of reduction in the volume of endolymph[106]. KCNQ1-KCNE1 channels are, in contrast, not prominent in adult musine ventricular function. Neonatal musine neonatal myocytes exhibit I_{Ks} and expression of both KCNQ1 and KCNE1

proteins[56,89,107]. Adult mouse ventricles express an adrenergic-sensitive steady-state current that is disrupted by *Kcnq1* deletion, does not involve KCNE1[108], and could potentially be generated by KCNQ1-KCNE2 complexes. *Kcne1* deletion reportedly causes atrial fibrillation in mice, and KCNE1 can be detected in adult mouse atria and conduction system[109], but it is not known which α subunit(s) KCNE1 regulates in these tissues in the mouse – Kv2.1 being one possibility.

Controversies and discrepancies (I). KCNE1 in the brain and kidneys

Typically not considered a neuronal complex, it was recently proposed that KCNQ1-KCNE1 channels may operate in some neurons, and that this could introduce a neural component to cardiac arrhythmias. Thus, mutations in KCNE1 or KCNQ1 might cause seizures that in turn trigger cardiac arrhythmias (perhaps exacerbated by the channels also being dysfunctional in the heart and therefore increasing arrhythmia susceptibility in the face of a trigger)[110]. Interestingly, *Kcnq1*$^{-/-}$ mouse hearts exhibit impaired repolarization *in vivo* but not when isolated, suggesting *Kcnq1*-linked LQTS in mice arises from an extracardiac source[106]. The controversy continues, centering on whether KCNE1 and KCNQ1 are actually expressed in neurons in mice and people.

Kcne1$^{-/-}$ mice exhibit altered salt and glucose homeostasis, and reduced NaCl consumption - the latter suggestive of a role for KCNE1 in mouse kidneys or salivary glands[111]. KCNQ1 and KCNE1 are expressed in mouse kidneys but they do not necessarily form a channel there, and the pharmacology and gating kinetics of K^+ currents in proximal convoluted tubule epithelial cells –where KCNE1 is expressed – are not consistent with KCNQ1-KCNE1 properties. Counterintuitively, the KCNQ1-preferential antagonist, chromanol 293B, had similar functional effects in the proximal tubule to those of *Kcne1* deletion, but this may reflect nonspecific action of chromanol 293B at the dosage used (100 μM). The cell-specific expression, biological functions and α subunit partners of KCNE1 in the kidneys remain a matter of debate[112–116]. KCNE1 was also previously suggested to form channels with KCNQ1 in the airway epithelium, but it now appears much more likely that KCNQ1-KCNE3 complexes are expressed there instead (see below)[117].

Physiological roles for KCNE3: the gut, airway and auditory neurons

KCNE3 is best known for its regulation of KCNQ1 in the intestine. KCNQ1-KCNE3 are located on the basolateral membrane of colonic crypt cells. Their constitutive activation and lack of inactivation enable them to provide a K^+ recycling conduit that facilitates electrogenic intestinal Cl^- secretion. All available evidence for the importance of this process is from the mouse, and specifically the *Kcne3*$^{-/-}$ mouse line, and there are currently no reported human disease associations linking KCNE3 (or KCNQ1) mutations to altered intestinal Cl^- secretion[17,118]. As mentioned above, estrogen downregulates intestinal KCNE3 expression, causing the water retention that occurs in female mice during proestrus. As observed for the intestine, *Kcne3* deletion in mice also disrupts tracheal Cl^- secretion, and basolateral KCNQ1-KCNE3 complexes are thought to be required for cAMP-stimulated Cl^- secretion in the airway epithelium. KCNQ1-KCNE3 channels may also facilitate Na^+

reabsorption in the airways of mice[117]. Again, data for the potential role of KCNQ1-KCNE3 in human airway epithelia are currently lacking.

In a different study of *Kcne3*$^{-/-}$ mice, a role for KCNE3 in auditory neurons was uncovered. KCNE3 was found to be expressed in spiral ganglion neurons (SGNs), with *Kcne3*$^{-/-}$ SGNs utilized as a convincing negative control for expression. *Kcne3* deletion age-dependently altered the firing properties and membrane potential variability of SGNs, and resulted in an increase in the transient outward current in these cells. Kv4.2, and not Kv4.3, was found to be expressed in both apical and basal SGNs, where it co-localized with KCNE3. Accordingly, KCNE3 was found to diminish Kv4.2 activity when the two were co-expressed in CHO cells[72]. Therefore, KCNE3 may act as a dampener for Kv4.2 activity in SGNs, permitting dynamic regulation of the transient K^+ current in these cells without the cell being required to remove Kv4.2 from the membrane, which might be too slow for the cells' requirements or too energetically costly. The functional effects in SGNs of *Kcne3* deletion were only observed during onset of hearing, during the first 12 days. At day 56, only two effects could be observed in SGNs – slightly enhanced afterhyperpolarizations of basal but not apical SGNs, and reduced interspike interval. Thus, KCNE3 might be more important during development of hearing than after auditory maturity, or else compensatory remodeling of other channels might lessen the deleterious consequences of *Kcne3* deletion over time[72].

Controversies and discrepancies (II). KCNE3 in the brain, muscle and auditory system

We previously found expression of KCNE3 transcript by Northern blot in all regions tested of human brain, and by RT-PCR from 12 DIV cultured rat primary hippocampal neurons isolated from embryonic stage 18 Sprague Dawley rats[68]. In addition, we detected KCNE3 protein by western blot in crude membrane preparations isolated from adult Sprague Dawley rat whole brains. We detected KCNE3-Kv2.1 and KCNE3-Kv3.1 complexes in these preparations, using co-immunoprecipitations. Our studies showed that endogenous KCNE3 co-localized with endogenous Kv2.1 but not Kv3.1 in cultured hippocampal neurons, while siRNA knockdown of endogenous KCNE3 in the PC12 cell line upregulated endogenous PC12 cell delayed rectifier K^+ current. Heterologous co-expression studies in CHO cells were consistent with the functional effects we had observed by knocking down endogenous KCNE3 in PC12 cells, i.e., KCNE3 slowed the activation of and downregulated Kv2.1 current (and downregulated overall activity but reduced inactivation of Kv3.1b)[68]. As mentioned above, KCNE3 was detected by others in auditory neurons, with the added advantage of having a *Kcne3*$^{-/-}$ negative control[72]. However, in contrast to our findings, Preston *et al* reported a failure to detect KCNE3 in mouse brain[118].

Similarly, Preston and colleagues reported a lack of KCNE3 expression in mouse skeletal muscle, and a lack of effects of *Kcne3* deletion on the skeletal muscle-related parameters they tested in mice: muscle morphology, spontaneous paralysis, myotonia, "movement", and rotarod performance[118]. Our studies of KCNE3 in skeletal muscle were driven by the findings of colleagues that the human KCNE3 R83H mutation is associated with periodic

paralysis – a skeletal muscle disorder in which sufferers experience bouts of debilitating paralysis. We detected *KCNE3* transcript by northern blot in human skeletal muscle, and found KCNE3 protein in rat sartorius muscle by western blot and in the mouse C2C12 myoblast cell line by western blot and immunofluorescence[65]. We determined that KCNE3 co-assembles with and functionally regulates Kv3.4, an N-type Kv channel α subunit known to be expressed in skeletal muscle, and that the R83H mutation in KCNE3, found to associate in individuals with periodic paralysis within two families, impaired function of Kv3.4-KCNE3 channels. Specifically, the mutant disrupted the ability of KCNE3 to left-shift the voltage dependence of Kv3.4 activation, leading to depolarization of resting membrane potential in skeletal myocytes[65]. We subsequently found that the R83H mutation also impairs the ability of KCNE3 to regulate other Kv channels[66]. Further, we found that the histidine introduced in this substitution makes Kv3.4-KCNE3 channels susceptible to block by protons, and could therefore make carriers particularly prone to impaired channel function during rest after exercise, when muscle pH drops drastically. Additionally, we showed that the neighboring residue, S82, is a serine phosphorylation site and that PKC phosphorylation of this residue is required for the left-shift in voltage dependence of Kv3.4 activation endowed by KCNE3[119]. However, the disease association has been highly controversial, with others finding the R83H sequence variant in unaffected individuals, raising the possibility that it is a benign polymorphism[120]. Another possibility is that carriers need another genetic 'hit' or specific environmental conditions to provoke paralysis[121].

Another controversy surrounds the possible association of KCNE3 (and KCNE1) with Ménière's disease – an inner ear disorder that manifests as tinnitus, periodic hearing loss, and spontaneous episodes of vertigo. Single nucleotide polymorphisms (SNPs) in *KCNE1* (112G/A, coding for the well-studied S38G polymorphism) and *KCNE3* (198T/C, a synonymous switch within the codon for F66) were found in one study to be enriched in Japanese Ménière's cohorts compared to unaffected individuals[122]. However, in a study of Caucasians, *KCNE1* and *KCNE3* SNPs were not found to associate with Ménière's[123]. Deep resequencing of KCNE3 in Caucasian people with chronic tinnitus failed to either support or disprove a link, with the authors concluding that more power was required[124]. While both genes are expressed in the auditory system (KCNE3 has been detected in auditory neurons, and all five KCNEs were detected in outer hair cells[78]), and KCNE1 is tightly associated with JLNS[23,85], establishing a firm link between human *KCNE3* sequence variation and auditory dysfunction will require further population or linkage studies.

Finally, not so much a controversy or necessarily a discrepancy, KCNE3 has been detected in human heart[104] (although the relative expression levels of KCNEs varies depending on the study[76,125] and may be affected by the sex of the donors, which was not always reported) and mutations in human *KCNE3* that disrupt its ability to inhibit Kv4.3 channels in human ventricle are thought to cause some cases of Brugada syndrome[74,126]. Human *KCNE3* mutations that cause gain-of-function of KCNQ1-KCNE3 channels are associated with atrial fibrillation, also suggested to arise from altered atrial myocyte channel activity[127]. Human *KCNE3* sequence variants associated with human disease are summarized in Table 3.

KCNE3 transcript was also detected in horse heart[43]. However, *Kcne3* was not detected in either the atria or ventricles of adult mice, by two different labs using different *Kcne3*$^{-/-}$

mouse strains as negative controls[118,128], and *Kcne3* deletion did not alter Kv currents in isolated ventricular myocytes[128]. Yet, *Kcne3* deletion predisposed to ventricular arrhythmogenesis in mice, lengthening the QT interval in older adults and predisposing to sustained ventricular tachycardias following ischemia/reperfusion[128]. The underlying mechanism is unprecedented, and involves hyperaldosteronism in *Kcne3*$^{-/-}$ mice associated with autoimmune attack on the adrenal glands. *Kcne3* is not expressed in mouse adrenals, but its deletion causes cytokines to be released that attract activated lymphocytes specifically to the adrenal glands. Administration of spironolactone, an aldosterone receptor antagonist, to *Kcne3*$^{-/-}$ mice ameliorated their QT prolongation and predisposition to ventricular tachycardia[128]. Two questions arise: first, what causes the adrenals in *Kcne3*$^{-/-}$ mice to release signals to attract activated B cells? Second, can this mechanism also be a component of human *KCNE3*-linked arrhythmogenesis? Resolution of these condundra will require further investigation.

Conclusions

In many ways, KCNE1 and KCNE3 represent the yin and yang of Kv channel regulation because of the often opposite yet complementary outcomes of their co-assembly with Kv α subunits. As more and more functional data emerge from studies of the KCNE family in expression systems and from mouse and human genetics studies, it becomes apparent that the KCNEs constitute a molecular toolkit that diversifies Kv channel functionality but also facilitates dynamic alteration of channel properties in response to other signaling elements – including membrane lipids, hormones, kinases and even larger membrane proteins such as solute transporters[129]. Their human disease associations will likely not be as common as those of the Kv α subunits for a variety of reasons – although in LQTS, base-for-base they match up rather well to α subunit genes in terms of population-wide contribution to pathogenicity[130]. Nevertheless, the phenotypes of *Kcne* null mice are fascinating and can inform us of their physiological roles and the consequences of their ablation (typically an altogether different lesion than a point mutation). Because KCNEs can alter Kv channel responses to native signals and also to pharmacological agents (in the context of both therapeutic targeting and side effects)[11,16,130–133], it behooves us to consider their presence in Kv and other channel complexes in different tissues, cell types and life stages, as they may yet provide a crucial ally in tuning drug specificity and efficacy.

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Abbreviations

AV block	atrioventricular block
BLAST	basic local alignment search tool
cAMP	*cyclic adenosine monophosphate*

Cav channel	voltage-gated calcium channel
CHO	Chinese Hamster ovary
di	drug-induced
ERRγ	estrogen-related receptor γ
EST	expressed sequence tag
fs	frameshift
HCN	hyperpolarization-activated, cyclic nucleotide-gated
HEK	human embryonic kidney
I_{Ks}/IsK	slowly activating K^+ current
JLNS	Jervell and Lange-Nielsen syndrome
KChIP	K^+ channel interacting protein
Kv channel	voltage-gated potassium channel
LQTS	Long QT syndrome
MiRP	MinK-related peptide
MTS	methanethiosulfonate
Nav channel	voltage-gated sodium channel
PIP_2	phosphatidylinositol 4,5-bisphosphate
PKA	protein kinase A
PKC	protein kinase C
QTc	QT interval corrected for heart rate
SGN	spiral ganglion neuron
SNP	single nucleotide polymorphism
SQTS	Short QT syndrome
TdP	torsade de pointes
TEVC	two-electrode voltage clamp
TM	transmembrane

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Highlights

- KCNE1 and KCNE3 regulate K^+ channel gating, voltage dependence and trafficking
- KCNE1 and 3 often have opposite effects on channel function, especially so for KCNQ1
- KCNE1-KCNQ1 channels are best known for their role in cardiomyocyte repolarization
- KCNE3-KCNQ1 channels are important in various secretory epithelia
- Human *KCNE1 and KCNE3* sequence variants cause various cardiac arrhythmias

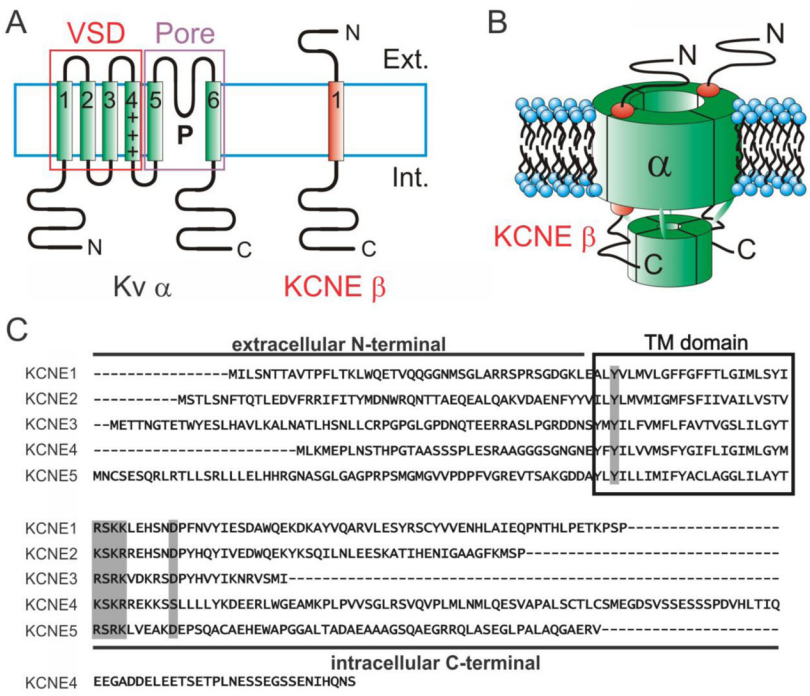

Figure 1. The KCNE gene family

A. *Left*, Topology diagram of a 6TM spanning Kv α subunit with voltage sensing domain (VSD) and pore domain highlighted. *Right*, 1TM topology of a KCNE subunit. Ext, extracellular; Int, intracellular.

B. 4:2 α:β stoichiometry of a KCNQ1-KCNE1 complex.

C. Sequence alignment of the KCNE gene family. Transmembrane (TM) domain boxed; highly conserved residues/features indicated with gray shading.

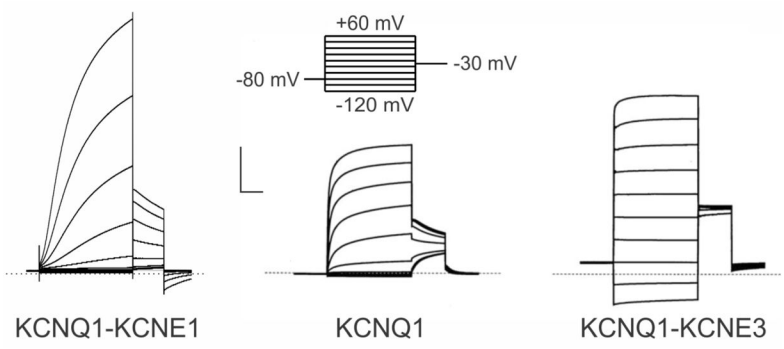

Figure 2. Functional effects of KCNE1 and KCNE3 on KCNQ1

Example traces recorded by two-electrode voltage clamp from oocytes injected with cRNA encoding KCNQ1 alone or with KCNE1 or KCNE3. Voltage protocol shown at top. Scale bars: vertical, 2 μA; horizontal, 1s. Dotted line indicates zero current level. Traces are from [3 and 47].

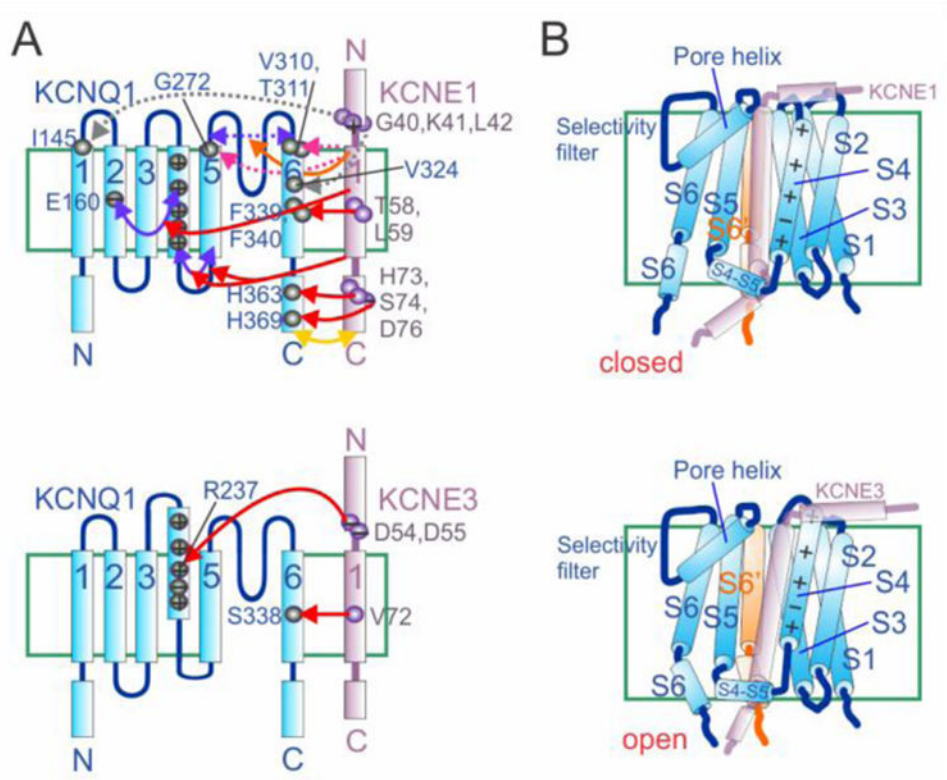

Figure 3. Mechanisms of KCNE1 and KCNE3 control of KCNQ1 gating and conductance

A. Topology diagrams of KCNQ1 with KCNE1 (*upper*) and KCNE3 (*lower*) showing residues (numbered where specific residues have been identified as particularly important) and domains identified as being influential in control of KCNQ1 gating by the KCNEs. Arrows: *red*, KCNE1 or 3 control of KCNQ1 activation; *yellow*, KCNE1 control of deactivation; *orange*, KCNE1 control of inactivation; *pink*, KCNE1 control of conductance; *purple*, inter-domain interactions within KCNQ1 that are affected by KCNE1; *dashed purple*, KCNQ1 outer vestibule/selectivity filter flexibility; *dashed gray*, physical proximity and/or interaction without major functional effects. "−" = acidic residue, "+" = basic residue. Citations appear in main text.

B. Cartoon of possible orientations with respect to KCNQ1 (*blue*), based on evidence summarized in panel A, of KCNE1 (*upper*) and KCNE3 (*lower*) at resting membrane potential. S6′ = the S6 of an adjoining KCNQ1 α subunit. KCNEs are depicted as semi-transparent to avoid concealing KCNQ1 features.

Table 1
Summary of main effects of KCNE1 and KCNE3 on Kv α subunits

See main text for expanded description of effects.

Kv α subunit	Effects of KCNE1	Effects of KCNE3
KCNQ1	Slows activation, strongly increases peak current in oocytes, CHO and HEK cells, and cardiac myocytes.[12,13]	Instantaneous activation, small increase in peak current in oocytes and CHO cells.[17,33]
KCNQ4	Mild upregulation in *Xenopus* oocytes.[67]	Inhibits in *Xenopus* oocytes.[17,78]
KCNQ5	Slows activation, increases peak current by decreasing inward rectification in HEK, oocytes. [77]	Inhibits in HEK cells and in *Xenopus* oocytes. [77]
hERG	Doubles current density in CHO cells.[61]	Strongly inhibits in *Xenopus* oocytes.[8]
Kv1.1	No effect in CHO cells.[69,70]	?
Kv1.1-Kv1.4	Increases current density 2-fold in CHO cells.[69,70]	?
Kv1.4	Traps in ER/Golgi in CHO cells. [69,70]	?
Kv2.1	Slows activation/deactivation in CHO cells.[57]	Slowed activation/deactivation in CHO cells.[76]
Kv3.1	Strongly slows activation/deactivation, accelerates inactivation in CHO cells.[71]	Weakly slows activation/deactivation, accelerates inactivation in CHO cells.[71]
Kv3.1-Kv3.2	Strongly slows activation/deactivation, accelerates inactivation in CHO cells.[71]	Weakly slows activation/deactivation, accelerates inactivation in CHO cells.[71]
Kv3.1-Kv3.4	Attenuates inactivation by “mopping” up homomeric Kv3.4 in CHO cells.[69,70]	?
Kv3.2	Strongly slows activation/deactivation, accelerates inactivation in CHO cells.[71]	Weakly slows activation/deactivation, accelerates inactivation in CHO cells.[71]
Kv3.3	Inhibits, probably by trapping in ER/Golgi in CHO cells.[69,70]	?
Kv3.4	Traps in ER/Golgi in CHO cells. [69,70]	Augments activity, left-shifts voltage dependence in CHO cells.[65]
Kv4.2	No effect (with α,β staggered injection) in *Xenopus* oocytes.[73]	Inhibits in CHO cells and In SGNs.[72]
Kv4.3	Slows gating, increases current in HEK cells.[75]	Inhibits in CHO cells.[74]
Kv4.3-KChIP2	Accelerates activation. Mildly speeds, slows recovery of, and left-shifts steady state inactivation; all in CHO cells.[76]	Accelerates activation. Strongly speeds, slows recovery of, and left-shifts steady state inactivation; all in CHO cells.[76]
Kv12.2	Inhibits in *Xenopus* oocytes.[67]	Inhibits *Xenopus* oocytes.[67]

Table 2

KCNE1 gene variants associated or putatively associated with human disease

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; n.r., not reported; RWS, Romano-Ward Syndrome; Sources include cited papers and [162]. KCNE1 gene accession number: P15382.

Mutation	**Disease**	***In vitro* cellular effects**
T7I	JLNS[85]	n.r.
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. [134,135]
T10M	LQT5[135]	n.r.
W17X	LQT5[135]	n.r.
G25V	Lone AF	I_{Ks} gain of function [95]
S28L	LQT5, AV block (neonatal)	n.r. [135,136]
R32H	LQT5	Gating not altered[135,137,138]
38G versus 38S	AF, AF in elderly patients, postoperative AF, LQT5	I_{Ks} loss of function, reduced membrane K_V7.1 (KvLQT1) channel[93,97,139–144]
38G versus 38S	Ménière's disease (Japanese cohort; not recapitulated in study of Caucasian population)[122,123]	n.r
V47F	LQT5	hERG Gain of Function[145]
L51H	LQT5	Does not process properly, not found in membrane[145]
G52R	LQT5	I_{Ks} reduced 50%[146]
G55S	LQT5[135]	n.r.
T58P	LQT5[135]	n.r.
L59P	LQT5[135]	n.r.
G60D	Lone AF	I_{Ks} gain of function; faster deactivation[95]
R67C	LQT5[135]	n.r.
R67H	LQT5[135]	n.r.
K70M	LQT5[135]	n.r.
K70N	LQT5[147]	n.r.
S74L D76N	LQT5 (JLNS+RW)[24] diLQTS[148]	D76N: I_{Ks} - smaller unitary currents and open probabilities; dominant negative[26] I_{Kr} – loss of function[145] S74L: I_{Ks} - loss of function[149]
N75-fs+34X	LQT5[135]	n.r.
Y81C	LQT5?	I_{Ks} loss of function, Positive shift for voltage of activation[150]
E83K	LQT5[135]	n.r.
D85N	LQT5? DiLQTS DiTdP	No effect on I_{Ks} $V_{1/2}$ of activation, or deactivation properties [148,151–159]
W87R	LQT5	I_{Ks} loss of function, altered gating[145]

Mutation	Disease	*In vitro* cellular effects
R98W	LQT5?	Disrupts I_{Ks} trafficking, right-shifts voltage dependence of activation[160]
V109I	LQT5	I_{Ks} loss of function (36%)[161]
Q117X	LQT5[135]	n.r.
T125M	LQT5[135]	n.r.
P127T	LQT5, RWS[137]	n.r.

Table 3

KCNE3 gene variants associated or putatively associated with human disease

AF, Atrial Fibrillation; BrS, Brugada Syndrome; fs, frame shift; LQTS, Long QT syndrome; n.r., not reported; Sources include cited papers and [162]. *KCNE3* Gene accession number: Q9Y6H6.

Mutation	Disease	*In vitro* cellular effects
T4A	LQTS? BrS	No effect on I_{Q1-E3} [163] I_{to} gain of function[126]
V17M	AF	K_V4.3 and Kv11.1 (hERG) gain of function [127]
R53H	AF	I_{Q1-E3} gain of function[164]
F66F (198T/C synonymous switch)	Ménière's disease (Japanese cohort; not recapitulated in study of Caucasian population) [122,123]	n.r.
R99H	BrS LQTS?	K_V4.3, I_{to} gain of function[74] I_{Q1-E3} Loss of function[163]
R83H	Periodic paralysis (but also detected in asymptomatic individuals in a later study)[65,120,121]	Kv3.4 loss of function and increased sensitivity to proton block[65]