Review

Molecular pathogenesis of long QT syndrome type 1

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ABSTRACT

Long QT syndrome type 1 (LQT1) is a subtype of a congenital cardiac syndrome caused by mutation in the KCNQ1 gene, which encodes the α-subunit of the slow component of delayed rectifier K^+ current (I_{Ks}) channel. Arrhythmias in LQT1 are characterized by prolongation of the QT interval on ECG, as well as the occurrence of life-threatening cardiac events, frequently triggered by adrenergic stimuli (e.g., physical or emotional stress). During the past two decades, much advancement has been made in understanding the molecular pathogenesis underlying LQT1. Uncovering the genotype-phenotype correlations in LQT1 is of clinical importance to better understand the gene-specific differences that may influence the propensity for developing life-threatening arrhythmias under specific conditions. Elucidation of these mechanisms will also help to improve the diagnosis and management of this cardiac disorder based on gene-specific considerations. This review describes the current medical consensus and recent developments regarding the molecular pathogenesis of LQT1 and provides a novel insight into the adrenergic regulation of this disease.

Contents

1. Introduction

Long QT syndrome (LQTS) is a potentially life-threatening arrhythmia characterized by delayed myocardial repolarization that produces QT prolongation on ECG, and an increased risk of torsades de pointes (TdP)-triggered cardiac events, such as syncope, cardiac arrest, and sudden cardiac death (SCD) [1,2]. This syndrome, with an estimated incidence of 1/2000 and a mortality rate of 21% for symptomatic patients not receiving therapy within one year from the first syncope event [1,3], includes congenital and acquired (e.g., drug-induced) conditions.

Molecular genetic studies have revealed that congenital LQTS is linked to mutations in genes encoding subunits of cardiac ion channels or adapter proteins that modify the channel functions.

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There are two types of inherited syndromes: autosomal dominant Romano-Ward syndrome [4] and autosomal recessive Jervell and Lange-Nielsen syndrome [5,6] that is usually associated with deafness [7]. In 1991, the Keating group reported for the first time that a single genetic locus on chromosome 11p15.5 was associated with LQTS within a single family [8]. Based on subsequent pioneering work [9–11], at least 15 types of genes have been found to be linked to 15 different types of LQTS (LQT1-15) to date.

In 1996, Wang et al. confirmed that type 1 congenital LQTS (LQT1) is caused by mutations in the *KCNQ1* (*KvLQT1*) gene, which is highly expressed in the heart and encodes a protein with structural features of a voltage-gated potassium channel [11]. Of the fifteen LQTS types, LQT1 is the most common and present in approximately 40–50% of all genotyped patients [12,13]. The *KCNQ1* gene encodes the α-subunit of the slow component of delayed rectifier K^+ current (I_{Ks}) channel (Kv7.1). This protein, together with the β-subunit KCNE1 and an adapter protein Yotiao, forms a macromolecular complex (i.e., the functional potassium ion channel I_{Ks}) [14,15]. The channel carries the major outward repolarizing K^+ current during the plateau phase of cardiac action potentials (APs) and plays a critical role in maintaining repolarization reserve in the heart [16,17]. Mutations in *KCNQ1* can cause dysfunction in the I_{Ks} channel, such as a delay in channel opening or a reduction in the duration for which it is open [8,16,18,19]. This results in a decrease in repolarizing K^+ current or a loss-of-function during phase 3 of the cardiac AP, which eventually causes QT prolongation and serious arrhythmias.

LQT1 can have numerous clinical manifestations, ranging from no symptoms to sudden cardiac death, which reflects the heterogeneity in channel dysfunction. Mutation type, location, and even a patient's ethnic background, age, and gender are critical factors that affect the pathophysiology of the disease [1]. A variety of studies have shown that LQT1 is more frequently triggered by adrenergic stimuli (e.g., physical exertion or emotional stress) compared with other forms of LQTS, particularly by diving and swimming [20–22]. Under normal physiological conditions, sympathetic activation promotes I_{Ks}, which shortens ventricular repolarization against the activation of L-type Ca^{2+} current and thereby protects against Ca^{2+}-related arrhythmogenicity [17]. When I_{Ks} is defective because of a *KCNQ1* mutation, the ventricular

repolarization or QT interval fails to shorten appropriately, thus creating a highly arrhythmogenic condition [1].

2. Molecular basis of LQT1

The LQT1-related *KCNQ1* gene is 404 kb long and located on chromosome 11p15.5. This gene codes for a 75-kDa protein containing 676 amino acids [11,23] and is mainly expressed in the heart, kidneys, small intestine, pancreas, prostate, and other non-excitable epithelial tissues [24]. It belongs to the Kv7 subfamily of voltage-gated K^+ channels (Kv) and shares a tetrameric architecture with all Kv channels. Each subunit contains six membrane-spanning segments (S1–S6 involving amino acid residues 122–348) connected by alternating intra- and extra-cellular loops, as well as a pore loop (amino acid residues 300–320) located between segments S5 and S6, with a cytosolic amino terminus (NH$_2$ terminus, residues 1–121) and a long cytosolic carboxyl terminus (COOH terminus, residues 349 to 676) (Fig. 1) [19,25,26]. The four subunits form a symmetrical alignment for the channel molecule together with KCNE1 (protein containing 129 amino acids with a single transmembrane segment) and Yotiao proteins, and construct a specialized pathway that allows for the conduction of potassium ions through water-filled pores located in the center of the complex. S1-S4 segments of the potassium channel form a voltage-sensing domain (VSD).

The S4 helix of KCNQ1 consists of a peculiar sequence of positively charged amino acids forming a region that is involved in sensing the membrane voltage and controlling the open probability of the channel [27]. In the resting state of the channel, these positively charged side chains are expected to be closer to the intracellular side of the membrane. Upon depolarization, effective charge motion within the membrane electric field toward the extracellular side of the membrane is accomplished through a series of conformational changes in the VSDs that lead to opening of the channel [28]. The pore region is composed of two transmembrane segments (S5 and S6) joined together by a linker (including a pore loop) that contains the conserved amino acids of the selectivity filter (residues 312–317) and affects the channel current amplitude, selectivity among ions, and channel blockade [29,30]. KCNQ1 possesses a large COOH terminus that is important
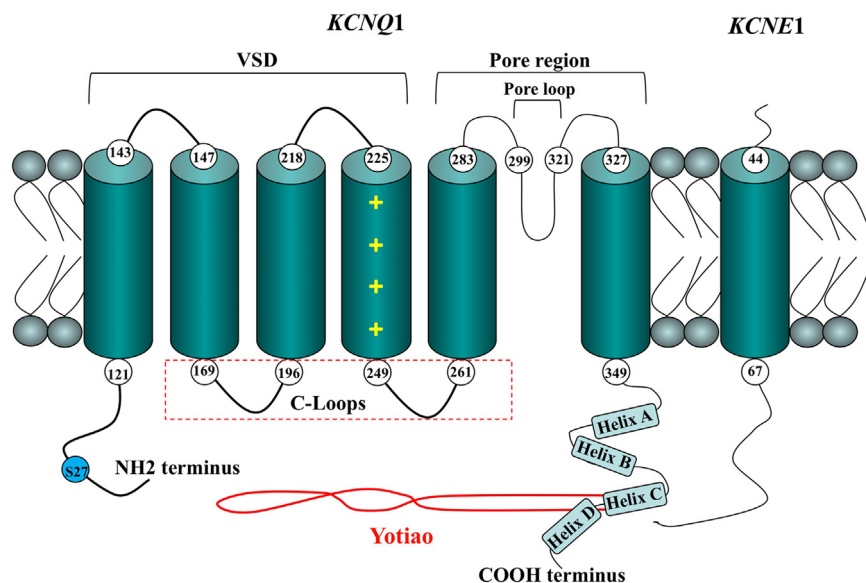

Fig. 1. Predicted topology of the I_{Ks} channel, which is formed by KCNQ1 and KCNE1 subunits and an adapter protein Yotiao. Each KCNQ1 subunit contains a NH$_2$ terminus, six membrane-spanning segments (S1–S6) including a pore loop and a voltage-sensing domain (VSD) (S1–S4), two cytoplasmic loops (S2–S3 and S4–S5), and a COOH terminus domain. The KCNE1 subunit contains a single α-helical transmembrane domain with an extracellular NH$_2$ terminus and a cytoplasmic COOH terminus domain.

for channel gating, assembly, and trafficking [19,31]. The COOH terminus is comprised of four amphipathic α-helices, coiled-coils, and clusters of basic amino acids. A and B proximal helices form sites for calmodulin (CaM) binding, whereas the distal coiled-coil helix C and helix D are responsible for tetramerization [19,31]. Helix C interacts with the KCNE1 distal COOH terminus and is thought to be a crucial region for modulation by phosphatidylinositol-4,5-bisphosphate (PIP₂), which acts to stabilize the open state of the channel [32]. A domain near the COOH terminus (residues 589–620) of KCNQ1 is responsible for subunit assembly specificity, and deletion of a part of this domain leads to impaired assembly of the channel complexes, followed by mistrafficking [33]. In the COOH terminus tail, a leucine zipper motif (residues 588–616) has been identified as the unique site through which A-kinase anchoring protein 9 (AKAP9, or Yotiao) targets protein kinase A (PKA) and protein phosphatase 1 (PP1) to the KCNQ1 complex [15]. Although the NH_2 terminus is relatively short, it contains an important residue (S27) that is critical for mediating the phosphorylation of KCNQ1 [15].

To date, over 250 mutations in *KCNQ1* have been found to be linked to LQT1 [34] and new LQT1 causing mutations continue to be identified. The vast majority of *KCNQ1* mutations are single nucleotide substitutions (missense) or small insertion/deletions that localize to the S1-S6 transmembrane domains [5,18,35,36]. One study assessing 600 LQT1 patients found that approximately 66.2% of *KCNQ1* mutations (75.3% of mutation carriers) were identified in the membrane-spanning segments (approximately 1/3 in the pore loop or adjacent transmembrane regions), 31.2% (24.3% of mutation carriers) in the C terminus, and only 2.6% (0.4% of mutation carriers) in the N terminus [18]. Importantly, these data are consistent with the results from another clinical study [25]. Mutations in the transmembrane, linker, and pore region of *KCNQ1* are usually defined as high-probability disease-causing mutations that tend to cause severe cardiac events in patients at younger ages compared to mutations in the COOH terminal region [37–41].

3. Genotype-phenotype correlations

Existing evidence to date indicates that genetic background may influence the severity of the disease. The mutation type, specific location, and degree of dysfunction play a critical role in the clinical course of LQT1. Moss et al. reported that LQT1 patients with transmembrane mutations and dominant-negative ion current effects had a longer corrected QT (QTc) interval and a higher frequency of cardiac events than individuals with mutations in other regions or mutations resulting in haploinsufficiency, and these genetic risks were independent of traditional clinical risk factors and drug therapy [18]. More recently, a retrospective study assessing genotype-phenotype correlations in 110 infant mutation carriers from LQT1 families also reported that carriers of the dominant negative Y111C mutation presented with a tendency towards more severe heart rate reduction and postnatal QTc prolongation than carriers of the R518X nonsense mutation [42].

Shimuzu et al. studied 95 patients carrying 27 *KCNQ1* mutations (19 in transmembrane regions and eight in the COOH terminus) [39]. They found that patients with transmembrane mutations had longer QTc, higher T-wave alterations, and more frequent LQTS-related cardiac events (including syncope, cardiac arrest, or sudden cardiac death) than those with C-terminal mutations, though the frequency of TdP was not different between the two study groups. In addition, most of the first cardiac events occurred before the age of 15 years in the LQT1 patients (particularly in males) with transmembrane mutations,

whereas only half of the LQT1 patients with C-terminal mutations suffered their first cardiac events before the age of 15.

Other retrospective data also indicate that missense cytoplasmic-loop mutations [43], pore mutations [36], and some specific point mutations, such as A341V, in *KCNQ1* [44,45] are associated with a longer QT interval and result in an increased risk of cardiac events and severe clinical phenotypes. In contrast to these studies, however, a study assessing 294 LQT1 patients with *KCNQ1* gene mutations demonstrated that there were no significant differences in clinical presentation, ECG parameters, and cardiac events among LQT1 patients by 40 years of age with *KCNQ1* mutations in different locations [46]. One possible explanation for this discrepancy is that the criteria for *KCNQ1* mutation type and position were different between their studies. LQT1 patients with transmembrane mutations (including those in the C-loop) were also found to be more sensitive to sympathetic stimulation and achieved a pronounced benefit from treatment with β-blockers compared to the patients with C-terminal mutations [43,47]. Therefore, the avoidance of strenuous exercise, in particular swimming, diving, or competitive sports, is recommended for LQT1 patients, especially younger males.

Silent mutations and compound mutations are also important genetic factors that affect the phenotype of LQT1. Approximately 25–36% of genetically positive patients with LQT1 may have a normal QTc range (defined as < 440 ms) without any clinical symptoms at rest [47,48]. Although these silent mutation-positive patients have a significantly lower risk of life-threatening cardiac events compared to those with phenotypic patterns, it should not be assumed that such a phenotype-negative individual who has a normal QTc is not affected by the cardiac disease. A number of risk assessments have confirmed that lethal arrhythmias can occur in these apparently healthy silent mutation carriers without any premonitory sign, especially during emotional stress or physical exertion [49–51]. There is also growing evidence that compound mutation carriers have a more severe cardiac phenotype compared with individuals carrying a single mutation [35,42,52–54]. Compound mutations were found to be associated with longer QTc, more frequent cardiac events, and earlier onset of cardiac events. Therefore, the management of patients with such mutations should be tailored to their increased risk for arrhythmias [55].

4. Genotype-I_{Ks} correlation

In 1996, Sanguinetti et al. and Barhanin et al. independently found that, when coassembled with the accessory subunit KCNE1, the KCNQ1 and KCNE1 complex could form a channel that very closely exhibited conductive and kinetic properties similar to that of cardiac I_{Ks} [14,56]. Kass and coworkers subsequently found that the targeting protein Yotiao, as a component of the macromolecular complex, is required to reconstitute cAMP-dependent regulation of I_{Ks} and provides a mechanistic link between the sympathetic nervous system and modulation of the cardiac action potential duration (APD) [15]. The KCNQ1 and KCNE1 subunits coassemble with Yotiao adapter into the cardiac I_{Ks}, and mutation in *KCNQ1*, *KCNE1*, or *AKAP9* (Yotiao) can cause functional reduction of I_{Ks} channels, leading to life-threatening cardiac arrhythmias corresponding to LQT1, LQT5, and LQT11, respectively.

Previous studies indicate that two distinct biophysical mechanisms mediate the reduced I_{Ks} current in patients with *KCNQ1* mutations: (1) coassembly or trafficking defects in which mutant subunits are not transported properly to the cell membrane and fail to incorporate into the tetrameric channel, with the net effect being a less than 50% reduction in channel function (haploinsufficiency); and (2) formation of defective channels involving mutant subunits with the altered channel protein

Before exercise
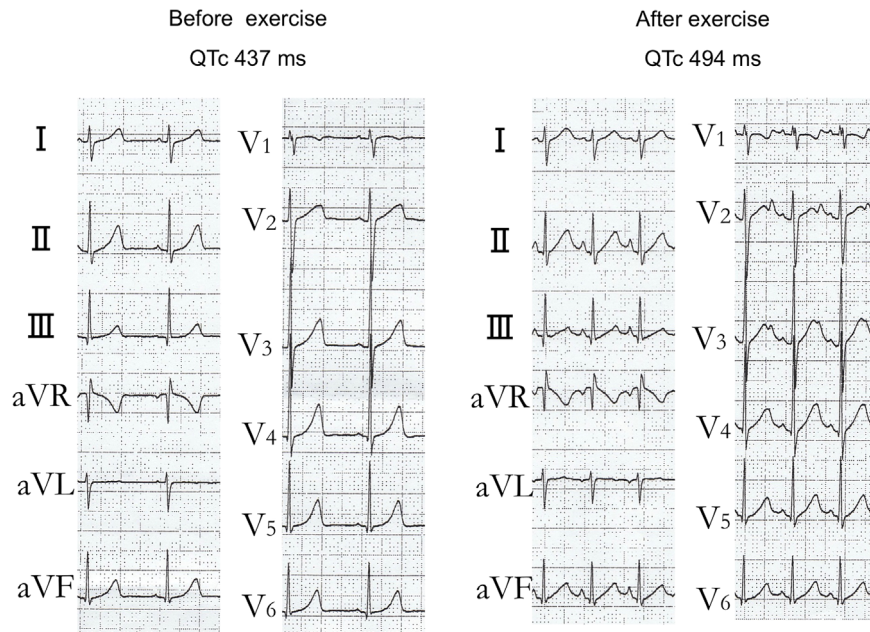QTc 437 ms

After exercise
QTc 494 ms

Fig. 2. Twelve-lead electrocardiograms (left: resting, and right: after exercise) in a 7-year-old boy carrying a *KCNQ1*-G269S mutation. QTc=corrected QT interval.

transported to the cell membrane, resulting in a dysfunctional channel having a greater than 50% reduction in channel current (dominant-negative effect) [18]. Recently, Mousavi et al. evaluated the functional properties of eight *KCNQ1* mutations that were identified in the S4 and S4-S5 linker (D242N, R243C, L250H), pore loop (G306V, D317N), and COOH terminus (L374fs+43X, N586D, L619M), respectively [7]. The results showed that D317N and L374fs+43X mutations exhibited a strong dominant-negative effect on KCNQ1-WT channel functions, which is consistent with previous findings for *KCNQ1* mutations located in the NH_2 terminus (Y111C), S2–S3 linker (R174C, A177P, Ala178fs/105, R190Q), S3-S4 (S225L), S4 domain (R243H), S5 domain (G269D, G269S, L272F), P-loop (Y281C, T311I, G314S, Y315S, Y315C, P320H, and P320A), S6 domain (ΔF339, L342F), and COOH terminus (R317N, R533W, R539W, R555H, K557E) [37,42,57–63]. The other mutations analyzed in that study were haploinsufficient for KCNQ1 channel function. Other reports have also indicated that membrane expression of the KCNQ1 channel protein can be reduced by trafficking defects in mutations located in the S2-S3 linker (A178T), S5 domain (ΔS276), pore loop (T322M), S6 domain (A336fs+16X), and COOH terminus (Y461X, R518X, A525T, Q530X, E543fs+107X, T587M, G589D, R594Q) [7,42,51,64–66].

The above data indicate that the correlation between the genotype and channel function in LQT1 is complicated and diversified. Even different mutations at the same position (e.g., *KCNQ1*-R243C and *KCNQ1*-R243H) cause different degrees of channel dysfunction. Moreover, not only do mutations with a dominant-negative effect occur in almost every location of the *KCNQ1* gene, but those with a trafficking defect exist in the main domains of the gene as well. However, the number of KCNQ1 pore-loop mutations causing a dominant-negative effect is much great than the number of mutations causing haploinsufficiency, suggesting that the pore-loop mutations are more commonly associated with severe electrophysiological and clinical phenotypes. Interestingly, Aizawa et al. found that the *KCNQ1* mutation Ala178fs/105 not only forms a hetero-multimer and causes a dominant-negative effect on the I_{Ks} channel, but that it also gives rise to a trafficking defect in the channel protein [63]. It is possible that both defective channel trafficking and defective channel formation mechanisms exist for some *KCNQ1* mutations simultaneously. Another correlation

between genotype and channel function has been described whereby some compound *KCNQ1* mutations (e.g., T391I/Q530X, A525T/R518X, and A178T/K422fs39X) severely disrupt channel trafficking [67].

In addition to inducing I_{Ks} dysfunction through dominant-negative loss-of-function effects and defective channel trafficking, mutations in *KCNQ1* suppress I_{Ks} channel function by reducing the channel affinity of interacting proteins [68,69]. Phosphatidy-linositol-4,5-bisphosphate (PIP_2) is a cofactor necessary for the activity of KCNQ1 channels [32,68,69]. It has been shown that intracellular PIP_2 regulates KCNQ1 channel activity in such a way that PIP_2 stabilizes the open state of the channels, which leads to an increased current amplitude, slowed deactivation kinetics, and a shift in the activation curve toward negative potentials. Park et al. showed that mutations in the S4 domain (R243H) and COOH terminus (R539W and R555C) increased the rate of dissociation of PIP_2 from the KCNQ1 channel, which decreased the number of open-state channels in the membrane [68]. Coyan et al. confirmed that R243H and R555C mutations cause an acceleration of KCNQ1 current rundown when membrane PIP_2 levels are decreasing. By observing the interaction of the *KCNQ1* R539W mutant with cholesterol, this group further suggested that the channel-cholesterol interaction might overcome the channel-PIP_2 interaction and stabilize the channel open-state [69].

5. Regulation by PKA

It is well known that cardiac events in LQT1 syndrome patients are more frequently triggered by adrenergic stimuli (e.g., physical or emotional stress) than those in other forms of LQTS. A clinical study of 371 LQT1 patients found that cardiac events were most common during exercise (62%) and emotional arousal (26%), while occasional during sleep or rest (3%) and from other triggers (9%) [20]. Approximately 35–36% of genotype-confirmed LQT1 patients have a normal QTc range without any clinical symptoms at rest [47,48], but lethal arrhythmias can occur in these apparently healthy silent mutation carriers without any premonitory sign, especially during adrenergic stimuli [49–51]. Recently, a heterozygous missense *KCNQ1* mutation G269S was identified in 11
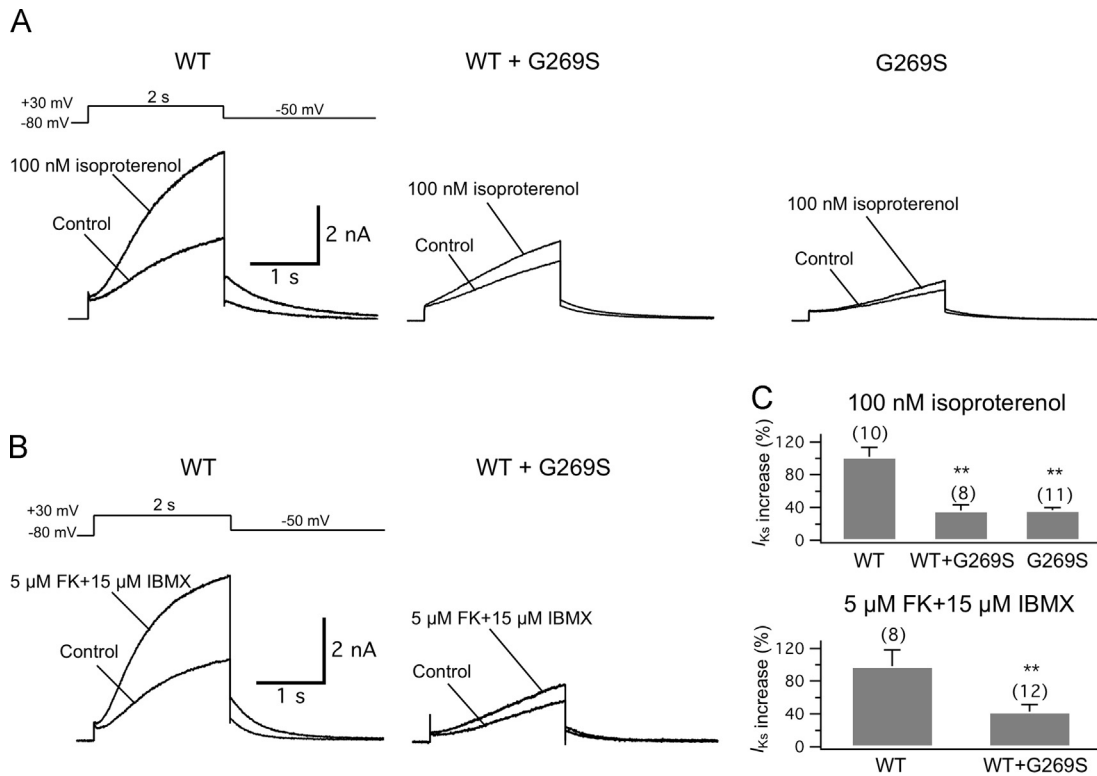
Fig. 3. I_{Ks} reconstituted with *KCNQ1*-G269S reduced responses to PKA stimulation. Superimposition of I_{Ks} traces recorded from human embryonic kidney 293 (HEK293) cells expressing Yotiao+KCNE1 with KCNQ1-WT, WT+G269S, and G269S before and after bath application of 100 nmol/L isoproterenol (A) or 5 mmol/L forskolin (FK)+15 mmol/L 3-isobutyl-L-methyl-xanthine (IBMX) (B). (C) The percentage increase in tail I_{Ks} after bath application of 100 nmol/L isoproterenol (upper) and 5 mmol/L FK+15 mmol/L IBMX (lower). **$p < 0.01$ *w.r.t.* KCNQ1-WT. PKA=protein kinase A.
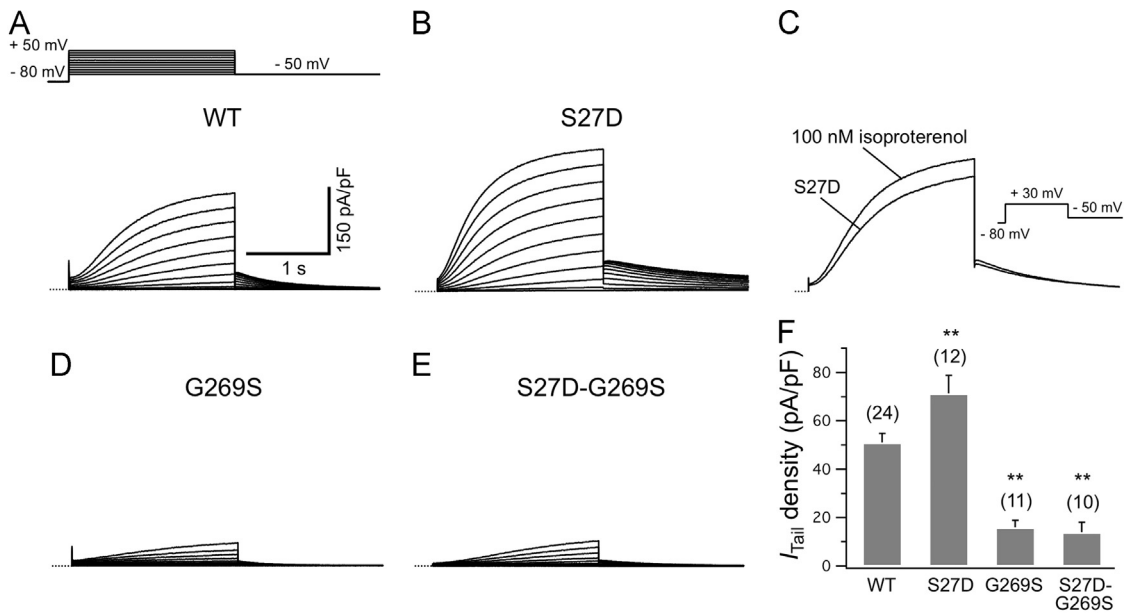

Fig. 4. G269S prevents the increase in I_{Ks} caused by the phosphomimetic S27D mutation. Representative current traces recorded from HEK 293 cells expressing Yotiao+KCNE1 with KCNQ1-WT (A), S27D (B), and exposure to 100 nmol/L isoproterenol (C), G269S (D), and S27D-G269S (E), respectively. (F) Bar graphs show effects of G269S on tail I_{Ks} densities recorded on repolarization to −50 mV following a 2-s depolarization to 30 mV for the different transfection conditions.**$p < 0.01$ *w.r.t.* KCNQ1-WT.

patients from four unrelated families. Most of the 11 patients had normal to borderline QTc intervals at rest, but had a significant QTc prolongation after exercise (Fig. 2). One family member had died suddenly and another one experienced syncope while dancing. Functional characterization of the I_{Ks} channel reconstituted with G269S in mammalian cells showed that the mutation modestly affected I_{Ks}, but severely blunted the increase in I_{Ks} after treatment with isoproterenol, pharmacological activators of PKA (Fig. 3), or in the PKA phosphomimetic mutation KCNQ1-S27D (Fig. 4), which mimics PKA-mediated phosphorylation of I_{Ks} channels. These findings provide important insight into the molecular mechanisms underlying adrenergic-induced LQTS and may explain why

patients with silent mutations exhibit an excessive prolongation of QT intervals during exercise. The results also suggest that beta-blocker therapy may have a beneficial effect in these patients.

In human ventricular myocytes, the I_{Ks} (outward current), rapid component of delayed rectifier K$^+$ current I_{Kr} (outward current), and L-type Ca^{2+} current $I_{Ca,L}$ (inward current) play a dominant role in the repolarization of APs and are the most important determinants of APD. Under physiological conditions, I_{Kr} and $I_{Ca,L}$, but not I_{Ks}, normally play a crucial role in controlling the ventricular AP at rest [70]. Therefore, KCNQ1 mutations (e.g., G269S) that cause a mild-to-moderate functional defect in I_{Ks} might ordinarily have little effect on the ventricular AP, which may explain why some KCNQ1 mutation carriers have normal to borderline QTc intervals with no or mild clinical symptoms at rest. In addition, the reason why individuals carrying a KCNQ1 mutation display a silent phenotype at rest may also be due to the "repolarization reserve" mechanism [71].

On the other hand, I_{Ks} plays a major role in regulating the ventricular AP after adrenergic stimuli (that upregulates I_{Ks} through cAMP-dependent PKA pathway) to prevent excessive ventricular APD or QT prolongation due to an $I_{Ca,L}$ increase [15, 72]. It is possible that the slow deactivation kinetics of I_{Ks} also contribute to the current upregulation through adrenergic stimuli. Due to the incomplete deactivation of I_{Ks}, there is residual activation at the onset of the succeeding AP that accumulates at fast rates, thus increasing the probability of the channel being in an open state [73].

Any abnormality causing a loss-of-function in the I_{Ks} macromolecular complex may lead to adrenergic-induced imbalance in ventricular repolarization currents and consequent QTc prolongation, which is identified based on the defective response of I_{Ks} to PKA stimuli due to mutations in KCNQ1 (-G269S, -A341V, and -K557E) [51,61,63], KCNE1-P127T [32], and Yotiao-S1570L [74]. Importantly, the role that I_{Ks} plays during adrenergic stimulation may explain why 88% of the cardiac events in LQT1 patients in the above study occurred during exercise and emotional stress [20].

6. Acquired LQT1

In addition to congenital pathology, LQTS can also be induced by a variety of stimuli, such as QT-prolonging medications, emotional stress, and strenuous exercise, especially under certain circumstances (risk factors). Of all triggers, QT-prolonging medications (e.g., antiarrhythmics, antihistamines, antibiotics, antidepressants, antipsychotics, and antiemetics) are the most common cause of acquired LQTS (aLQTS), which is believed to be related to drug-induced I_{Kr} channel block [71]. Due to unique pore structural properties (spacious inner cavity and aromatic drug-binding sites in the S6 domain facing the inner cavity), the I_{Kr} channel displays an unusual susceptibility to a wide range of structurally diverse compounds that interact with the pore.

Risk factors for aLQTS include electrolyte disturbances (e.g., hypokalemia, hypomagnesemia), bradycardia, gender, heart disease, and liver insufficiency. Moreover, genetic mutations in major LQTS-related genes including KCNQ1 have also been shown to be involved in aLQTS [75–78]. Siebrands et al. reported that the KCNQ1-A344V mutation increased the susceptibility of I_{Ks} channel to a local anesthetic bupivacaine, while the mutation per se did not cause a severe clinical phenotype of LQT1 [77]. Veerman et al. reported that the KCNQ1-K422T mutation per se had a mild clinical phenotype of LQT1, but additional fluoxetine or norfluoxetine resulted in more prominent QTc prolongation in the mutation carriers [78]. Electrophysiological study demonstrated that both fluoxetine and norfluoxetine inhibited KCNQ1/KCNE1 currents in HEK293 cells [78]. The above studies suggest that loss-of-function

in I_{Ks} caused by KCNQ1 mutation not only can predispose patients to congenital LQT1, but can be also associated with acquired LQT1. Normal cardiac repolarization critically depends on the interplay of multiple ion currents, and these provide some redundancy or "reserve", which protects against excessive QT prolongation and allows for an LQTS mutation to remain clinically silent or mild. The lesions in these repolarizing mechanisms can reduce "repolarization reserve" and therefore increase the risk for aLQTS [71]. The loss-of-function in I_{Ks}, which is a major repolarization current, occurs due to a KCNQ1 mutation and decreases the repolarization reserve [16,17,71,77]. However, this may be insufficient to elicit a full-blown LQT1 phenotype, especially at rest. When a pathologic trigger such as an I_{Ks}-blocking and/or I_{Kr}-blocking medication is present, the superimposition of lesions will produce marked AP prolongation and lead to acquired LQT1. In fact, the adrenergic-induced latent LQT1 is a type of aLQTS, which is triggered by sympathetic stimuli.

7. Conclusions

Uncovering the molecular pathogenesis of LQT1 is helpful, and even mandatory, for precise diagnosis, risk stratification, and management of LQT1 patients. Although some progress has been achieved in investigating the genotype-phenotype correlation through protracted and unremitting efforts, our current understanding of the molecular pathogenesis remains incomplete and sometimes fails to allow for translating the genotype-phenotype correlation into clinical reality. Moreover, neither the localization of a KCNQ1 mutation nor its cellular electrophysiological effect is sufficient to predict the impact on clinical manifestations.

The reasons why individuals (even from the same family) carrying the same mutation (e.g., KCNQ1-A341V and KCNQ1-R231C) exhibit diverse cardiac phenotypes clinically remain unknown. The findings to date indicate that mechanisms underlying LQTS are not only multifactorial, but are also involved in pathway crosstalk. Some recent studies show that protein kinase C and the parasympathetic nervous system are also involved in the control of clinical phenotypes in LQT1 [79,80], which brings in a new view to uncovering pathogenic mechanisms underlying the inherited arrhythmia. In addition, the use of induced pluripotent stem cells may better elucidate the clinical heterogeneity in LQTS, especially in cases that have compound mutations.

Conflict of interest

All authors declare no conflict of interest related to this study.

Acknowledgments

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