Molecular pathogenesis of long QT syndrome type 1

Jie Wu, PhD, Wei-Guang Ding, MD, PhD, Minoru Horie, MD, PhD

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\textsubscript{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.

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 2% 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.
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 (Iₖₛ) 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 Iₖₛ) [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 Iₖₛ 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 Iₖₛ, which shortens ventricular repolarization against the activation of L-type Ca²⁺ current and thereby protects against Ca²⁺-related arrhythmogenicity [17]. When Iₖₛ 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 (NH₂ 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...
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 KCN1 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 NH2 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% 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].

Shimizu 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, they 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-Iks 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 Iks [14,56]. Kass and coworkers subsequently found that the targeting protein Yotiao, as a component of the macro-molecular complex, is required to reconstitute cAMP-dependent regulation of Iks 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 Iks, and mutation in KCNQ1, KCNE1, or AKAP9 (Yotiao) can cause functional reduction of Iks 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 Iks 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
transferred 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, R376X, R425fs, L619M), respectively [7]. The results showed that D317N and L374fs + 43X mutations exhibited a strong dominant-negative effect on KCNQ1-W7 channel functions, which is consistent with previous findings for KCNQ1 mutations located in the NH2 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, G503X, 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 greater 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 Iks 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 Iks dysfunction through dominant-negative loss-of-function effects and defective channel trafficking, mutations in KCNQ1 suppress Iks channel function by reducing the channel affinity of interacting proteins [68, 69]. Phosphatidylinositol-4,5-bisphosphate (PIP2) is a cofactor necessary for the activity of KCNQ1 channels [32, 68, 69]. It has been shown that intracellular PIP2 regulates KCNQ1 channel activity in such a way that PIP2 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 PIP2 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 PIP2 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-PIP2 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. 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.
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

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-1-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 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, \( I_{Ks} \) and \( I_{Ca,L} \) but not \( I_{Kr} \) 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, \( I_{Ca,L} \) plays a major role in regulating the ventricular AP after adrenergic stimuli (that upregulate \( I_{Ks} \) 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 \( I_{Ks} \) macro-molecular 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, anthistamines, antibiotics, anti-depressants, antipsychotics, and anti-epileptics) are the most common cause of acquired LQTS (aLQTS), which is believed to be related to drug-induced \( I_{Ks} \) 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 \( I_{Ks} \) 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 also be 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

This study was supported by the National Natural Science Foundation of China (Nos. 81273501 and 81470378).

References

[1] Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol 2012;5:868–77.
[2] Boden DM. Clinical practice: long-QT syndrome. N Engl J Med 2008;358:169–76.
[3] Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009;120:1761–7.
[4] Romano C, Genome G, Pongiglione R. Aritmie cardiache rare dell’eta pediatrica. Clin Pediatr 1963;45:658–83.
[5] Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103–6.
6. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT-interval and sudden death. Am Heart J 1957;54:59–68.

7. Moussavi Nik A, Charaie S, Jeong Kim H. Cellular mechanisms of mutations in Kv71: auditory functions in Jervell and Lange-Nielsen syndrome vs Romano-Ward syndrome. Front Cell Neurosci 2015;9:1–14.

8. Keating M, Atkinson D, Dunn C, et al. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. Science 1991;252:704–6.

9. Curran ME, Slepian I, Timothe KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.

10. Wang Q, Shen J, Slepian I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995;80:805–11.

11. Wang Q, Curran ME, Slepian I, et al. Positional cloning of a novel potassium channel gene: KVLOQT1 mutations cause cardiac arrhythmias. Nat Genet 1996;12:17–23.

12. Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 2005;294:2975–80.

13. Shimizu W, Horie M. Phenotypic manifestations of mutations in genes encoding subunits of cardiac potassium channels. Circ Res 2011;109:97–109.

14. Wang J, Curran ME, Szabo A, et al. Coassembly of KVLQT1 and mink (Isk) proteins to form cardiac I(Ks) potassium channel. Nature 1996;384:80–3.

15. Marx SO, Kurokawa J, Reiken S, et al. Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. Nat Medicine 2002;295:496–9.

16. Jost N, Virag L, Comtois P, et al. Ionic mechanisms limiting cardiac repolarization reserve in humans compared to dogs. J Physiol 2013;591:4189–4206.

17. Sanguinetti MC, Long QT syndrome: ionic basis and arrhythmia mechanism in long QT syndrome type 3. J Cardiovasc Electrophysiology 2000;11:710–2.

18. Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type 1-long QT syndrome by location, coding type, and biological function of mutations involving the KCNQ1 gene. Circulation 2007;115:2481–491.

19. Dvir M, Peretz A, Haitin Y, et al. Recent molecular insights from mutated KCNQ1-delta F339 potassium channels linked to Romano-Ward syndrome. Cardiovasc Res 2005;67:487–94.

20. Schwartz PJ, Priori SG, Napolitano C, et al. Risk stratification for sudden death in the long QT syndrome. J Cardiovasc Electrophysiology 2005;156:1185–1206.

21. Spatjens RL, Bebarova M, Seyen SR, et al. Long-QT mutation p.K557E-Kv7.1: Dominant-negative I(Ks) suppression of KCNQ1-KCNE1 potassium channels linked to hereditary long QT syndrome with phenotypic variability. PLoS One 2013;8:e74017.

22. Takeda Y, Ihara K, Shimizu W, et al. Dominant-negative control of cAMP-Ca2+/calmodulin-dependent protein kinase IImediated I(Ks) regulation by PKA and PIP2. J. Biol Chem 2005;280:29654–62.

23. Aizawa Y, Ueda K, Wu L, et al. Truncated KCNQ1 mutant, A178fs/105, forms a functional potassium channel with impaired gating and reduced activity. Biochemistry 2012;51:9076–85.

24. Wimo A, Fosdal I, Lindh M, et al. Third trimester fetal heart rate predictions improve in the presence of metabolic and mechanical burden in the type 1 long QT syndrome. Circ Arrhythm Electrophysiol 2015 pii: CIRCEP.14.002552. [Epub ahead of print].

25. Bardshey A, Goldenberg I, Uchi J, et al. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: Implications for mutation-specific risk stratification and beta-blocker therapy in type 1-long QT syndrome. Circulation 2012;125:1988–96.

26. Brink PA, Crotti L, Corfield V, et al. Phenotypic variability and unusual clinical severity of congenital long QT syndrome in a founder population. Circulation 2005;112:2602–10.

27. Crotti L, Spazzolini C, Schwartz PJ, et al. The common long-QT syndrome mutation KCNQ1/A431V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: toward a mutation-specific risk stratification. Circulation 2007;116:2366–75.

28. Zizakiewicz M, Moss SE, Sheu G, et al. Location of mutation in the KCNQ1/long QT syndrome genetic testing. Heart Rhythm 2005;2:507–14.
Coyan FC, Abderemane-Ali F, Amarouch MY, et al. A long QT mutation substitutes cholesterol for phosphidylinositol-4,5-bisphosphate in KCNQ1 channel regulation. Plos One 2014;9:1–12.

Jost N, Virág L, Bitay M, et al. Restricting excessive cardiac action potential and QT prolongation: a vital role for I_Ks in human ventricular muscle. Circulation 2005;112:1392–9.

Roden DM. Long QT syndrome: reduced repolarization reserve and genetic link. J Intern Med 2006;259:59–69.

McDonald TF, Pelzer S, Trautwein W, et al. Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. Physiol Rev 1994;74:365–507.

Viswanathan PC, Shaw RM, Rudy Y. Effects of I_{Kr} and I_{Ks} heterogeneity on action potential duration and its rate dependence: a simulation study. Circulation 1999;99:2466–74.

Chen L, Marquardt ML, Tester DJ, et al. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. Proc Natl Acad Sci USA 2007;104:20990–5.

Itoh H, Crotti L, Aiba T, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. Eur Heart J 2015 pii: ehh695. [Epub ahead of print].

Itoh H, Sakaguchi T, Ding WG, et al. Latest genetic backgrounds and molecular pathogenesis in drug-induced long-QT syndrome. Circ Arrhythm Electrophysiol 2009;2:511–23.

Siebrants CC, Binder S, Eckhoff U, et al. Long QT1 mutation KCNQ1 A344V increases local anesthetic in sensitivity of the slowly activating delayed rectifier potassium current. Anesthesiology 2006;105:511–20.

Veerman CC, Verkerk AO, Blom MT, et al. Slow delayed rectifier current blockade contributes importantly to drug-induced long QT syndrome. Circ Arrhythm Electrophysiol 2013;6:1002–9.

Porta A, Girardengo G, Bari V, et al. Autonomic control of heart rate and QT interval variability influences arrhythmic risk in long QT syndrome Type 1. J Am Coll Cardiol 2015;65:367–74.

Matarel A, Medei E, Lopes CM. PKA and PKC partially rescue long QT type 1 phenotype by restoring channel-PIP2 interactions. Channels 2010;4:3–11.