Therapeutic Strategies for Long-QT Syndrome
Does the Molecular Substrate Matter?

Yanfei Ruan, MD; Nian Liu, MD; Carlo Napolitano, MD, PhD; Silvia G. Priori, MD, PhD

The discovery of genetic defects underlying long-QT syndrome (LQTS) has allowed to identify important genotype-phenotype correlations that are now being used for risk stratification. The next challenge is to exploit the new information on the pathophysiology of the disease derived from molecular genetics to devise more effective therapies. The successful response of LQT1 patients to β-blockers, the QT-shortening action of sodium channel blockers in at least some LQT3 patients, and the importance of maintaining adequate plasma potassium levels in LQT2 patients clearly demonstrate the importance of selecting therapy in the context of the molecular substrate.

The hurdles on the road toward the development of novel therapeutic strategies are represented by the variable expressivity of the disease, the high prevalence of “private” mutations, and the role of genetic and nongenetic factors that act as modifiers of the phenotype. Given the large number of mutations identified and their phenotypic complexity, it is clearly impossible to anticipate a scenario in which each mutation will be managed through a specific therapy. However, the evidence that mutations in the LQTs gene may be clustered based on their electrophysiological profile and on their response to specific drugs may provide the rationale for the development of mutation-specific therapies.

In this article, we will review the most relevant genotype-phenotype features of LQTS and the strategies explored to develop novel therapeutic approaches.

LQTS: An Increasingly Complex Scenario

Definition and Prevalence

The congenital LQTS is an inherited arrhythmogenic disease characterized by abnormally prolonged QT interval leading to life-threatening arrhythmias in the presence of a structurally normal heart.1 Different clinical variants of LQTS have been identified. Romano Ward syndrome, transmitted as an autosomal dominant trait, is the most common form of LQTS and presents only a cardiac phenotype. Less prevalent variants of LQTS, such as Andersen and Timothy syndromes or the recessive Jervell and Lange-Nielsen syndromes, also present extracardiac abnormalities.

There are no systematic studies on LQTS prevalence in the general population. Indirect estimates portray a prevalence between 1 in 3000 and 1 in 10 000.1 However, given that 10% to 35% of LQTS patients presents with a normal QTc interval and that 3% to 4% of probands inherit 2 independent mutations form nonconsanguineous parents,1,2 it is likely that the actual prevalence is probably higher.

Drug-induced LQTS is an iatrogenic response to drugs that mimics congenital LQTS. Because of the phenotypic overlapping, it was originally thought that a large proportion of drug-induced LQTS could manifest in carriers of incompletely penetrant mutations located on genes linked to congenital LQTS.3 Today, it is clear that <10% of patients with drug-induced LQTS harbor mutations in 1 LQTS gene.4

Genetic Bases

The presence of a LQTS genetic mutation leads to electric instability. Arrhythmias, typically polymorphic ventricular tachycardia with Torsades de Pointes morphology, are thought to be caused by triggered activity elicited by adrenergic activation.1 The initial molecular studies suggested that all genes linked to the LQTS phenotype encode for proteins encoding various subunits of transmembrane ion channels. More recently, genes that code for proteins that exert a regulatory function on ion channels have been also linked to LQTS (Table), thus expanding the complexity of the disease. Nonetheless, the concept that LQTS genes ultimately affect ionic currents, either directly (ion channel mutations) or indirectly (chaperones and other modulators), still holds true.

Mutations in potassium-channel genes such as KCNQ1 (LQT1) and KCNH2 (LQT2) and in the sodium-channel gene SCN5A (LQT3) were the first genetic causes of LQTS to be identified. The LQT1–3 variants constitute the 3 major forms of LQTS (Table), thus expanding the complexity of the disease. Nonetheless, the concept that LQTS genes ultimately affect ionic currents, either directly (ion channel mutations) or indirectly (chaperones and other modulators), still holds true.

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<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Chromosomal Locus</th>
<th>Gene Symbol</th>
<th>Protein (Symbol)</th>
<th>Current</th>
<th>In Vitro Characterization</th>
<th>Gene-Specific Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>IKs potassium channel α-subunit (KvLQT1)</td>
<td>↓ IkS</td>
<td>Dominant negative suppression, trafficking defect, abnormal gating, reduced response to β-AR signal</td>
<td>β-blockers,† potassium channel openers†</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35-q36</td>
<td>KCNH2</td>
<td>IKr potassium channel α-subunit (HERG)</td>
<td>↓ IkR</td>
<td>Dominant negative suppression, trafficking defect, abnormal gating</td>
<td>β-blockers,† potassium supplement,† potassium channel openers, fexofenadine and thapsigargin</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21</td>
<td>SCN5A</td>
<td>Cardiac sodium channel α-subunit (Nav 1.5)</td>
<td>↑ Ina</td>
<td>Abnormal gating; sustained current, slower inactivation, faster recovery, increased window current</td>
<td>Sodium channel blockers (mexiletine)†</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25-q27</td>
<td>ANK2</td>
<td>Ankyrin B, (ANK9)</td>
<td>↓ Ncx1, Na/K ATPase, InsP3</td>
<td>Loss of expression and mislocalization</td>
<td>None proposed</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1-22.2</td>
<td>KONE1</td>
<td>Iββ potassium channel β-subunit (Mink)</td>
<td>↓ Ikβ</td>
<td>Dominant negative suppression, abnormal gating, reduced response to β-AR signal</td>
<td>β-blockers, potassium supplement, potassium channel openers</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22.1-q22.2</td>
<td>KONE2</td>
<td>IKr potassium channel beta subunit (MIRP)</td>
<td>↓ IkR</td>
<td>Reduced current density and abnormal channel gating</td>
<td>β-blockers, potassium supplement, potassium channel openers, fexofenadine and thapsigargin</td>
</tr>
<tr>
<td>LQT7/Andersen</td>
<td>17q23.1-q24.2</td>
<td>KCNJ2</td>
<td>IK1 potassium channel (Kir 2.1)</td>
<td>↓ IK1</td>
<td>Dominant negative suppression, nonfunctional channels, trafficking defect, abnormal gating</td>
<td>None proposed</td>
</tr>
<tr>
<td>LQT8/Timothy</td>
<td>12p13.3</td>
<td>CACNA1c</td>
<td>Voltage-gated calcium channel, CaV1.2</td>
<td>↑ ICa</td>
<td>Loss of inactivation</td>
<td>Calcium channel blockers†</td>
</tr>
<tr>
<td>LQT9</td>
<td>3p25</td>
<td>CAV3</td>
<td>Caveolin-3</td>
<td>↑ Ina</td>
<td>Increased late inactivation</td>
<td>Sodium channel blockers (mexiletine)</td>
</tr>
<tr>
<td>LQT10</td>
<td>11q23</td>
<td>SCN4B</td>
<td>Cardiac sodium channel β-4 subunit</td>
<td>↑ Ina</td>
<td>Increased late inactivation</td>
<td>Sodium channel blockers (mexiletine)</td>
</tr>
<tr>
<td>LQT11</td>
<td>7q21-22</td>
<td>mAKAP</td>
<td>A-kinase anchoring proteins</td>
<td>↓ IkS</td>
<td>Reduced phosphorylation of the Ikβ channel</td>
<td>β-blockers</td>
</tr>
<tr>
<td>LQT12</td>
<td>20q11.2</td>
<td>SYN1</td>
<td>Syntrophin</td>
<td>↑ Ina</td>
<td>Increased late inactivation</td>
<td>Sodium channel blockers (mexiletine)</td>
</tr>
</tbody>
</table>

NCx indicates sodium calcium exchanger; Na/K ATPase, sodium potassium ATP pump; InsP3, inositol 3-phosphate receptor; β-AR, β-adrenergic receptor.

*Possible gene/mechanism-specific therapies are reported based on known pathophysiology.
†Experimentally or clinically tested therapies.
As of today, 12 LQTS genes have been identified (Table). Some of these genes (ankyrin B, caveolin-3, A-kinase anchoring proteins, and syntrophin) cause LQTS by altering the intracellular protein localization, the ion channels gating, the response to the sympathetic stimulation, or nitrosylation of ion channels.\(^5\)\(^-\)\(^8\) Despite the possible bias due to the lack of systematic assessments, the “newer” LQTS genes seem to affect a minority of patients (1% to 3% each). For this reason, the natural history, genotype-phenotype correlation, and response to therapy are still undefined.

**Genetic Influence on Clinical Presentation and Natural History**

Genetics has profoundly modified the clinical management of LQTS. Indeed, together with gender and QT-interval duration, the genetic background is an independent predictor of cardiac events before therapy.\(^9\) Furthermore, genotype-phenotype studies have clearly highlighted the correlation between genetic heterogeneity (multiple genes associated with the LQTS phenotype) and phenotypic pleiotropy (ie, the spectrum of the clinical and cellular phenotypes), and they have resulted in the development of gene-specific recommendations for risk stratification and management. Moss et al\(^10\) were the first to suggest that the genetic background could determine distinct phenotypes when they reported LQT1-, LQT2-, and LQT3-specific ST-T morphologies. Further quantification of this aspect showed that the sensitivity of ECG analysis in identifying the genetic substrate is as high as 85% and 83% (in LQT1 and LQT2, respectively) but unsatisfactory for LQT3 (43%).\(^11\) Subsequently, several other observations were added to compose the distinguishing profile for each of the 3 most common LQTS variants (Figures 1 through 3).

LQT1 is the most frequent genetic form of LQTS, and it accounts for 30% to 35% of LQTS cases. LQT1 patients experience most cardiac events (62%) during exercise (swimming seems a common trigger for cardiac events in LQT1), whereas only 3% of the arrhythmic episodes occur during rest/sleep.\(^12\)\(^,\)\(^13\) Thus, given the pivotal role of catecholamines in precipitating arrhythmias in LQT1, antiadrenergic inter-

![Figure 1. Clinical presentation of LQT1, including the typical ST-T wave morphology (A), penetrance and cardiac event rate (B), and triggers for lethal cardiac events (C). Data are from references 2, 9, 12, and 14. CA indicates cardiac arrest.](Image)

![Figure 2. Clinical presentation of LQT2, including the typical ST-T wave morphology (A), penetrance and cardiac event rate (B), and triggers for lethal cardiac events (C). Data are from references 2, 9, 12, and 14. CA indicates cardiac arrest.](Image)

![Figure 3. Clinical presentation of LQT3, including the typical ST-T wave morphology (A), penetrance and cardiac event rate (B), and triggers for lethal cardiac events (C). Data are from references 2, 9, 12, and 14. CA indicates cardiac arrest.](Image)
Genotype Based Therapy in LQTS

Mechanisms Underlying Potassium-Dependent LQTS

The KCNQ1 (LQT1) gene encodes for the α-subunit of the slowly activating component of the IKs current potassium channel (Table) that is the slow component of the IK, a major repolarizing current during phase 3 of the cardiac action potential. This α-subunit (KvLQT1) is a transmembrane protein with 6 transmembrane segments. Homotetrameric assembly is required to recapitulate the functional channel. The α-subunits coassemble with the small β-subunits encoded by the KCNE1 gene. IKs current increases on catecholamine stimulation. Therefore, a loss of IKs leads to the inability to adapt (shorten) action potential duration on tachycardia and to the related increase of arrhythmias elicited by physical activity.

Interestingly, Chen et al recently reported one A-kinase anchoring protein (AKAP9 or Yotiao) mutation in LQTS. Yotiao mediates protein kinase A phosphorylation of the channel, and the reported S1570L mutation eliminates the functional response of the IKs channel to cAMP, leading to action potential prolongation.

KCNH2 is the gene involved in LQT2. The encoded protein human ether-a-go-go-related gene (HERG) constitutes the α-subunit of the channel conducting the IKr current. Likewise for KvLQT1, HERG is a transmembrane protein with 6 membrane spanning segments that forms homotetramers that coassemble with β subunits.

KCNQ1 and KCNH2 mutations lead to a loss of protein function, thus prolonging the QT interval. Such potassium current impairment is obtained through multiple biophysical mechanisms. The integration of mutant proteins in the tetrameric complexes may impact on the function of the wild-type protein: the so-called “dominant negative effect” that causes a greater than the expected 50% (for a heterozygous condition) reduction of current. Alternatively, mutations may lead to truncated proteins that cannot coassemble with the wild type; therefore, their functional defect is mainly due to a reduced production of α subunits that determines a 50% current reduction (haploinsufficiency).

Recently, Gong et al showed that nonsense mutations present a decrease in mutant mRNA transcripts via nonsense-mediated mRNA decay, which prevents the production of truncated proteins, if present in the myocytes could exert a deleterious dominant-negative effect. Some of the mutants do not affect functional properties of channels but they rather interfere with the localization of the protein in the membrane; this behavior is often referred to as “defective intracellular trafficking.” Rescue of trafficking abnormalities is one of the gene-specific therapeutic strategies that are being investigated for LQT2 patients.

Gene-Specific Therapy in LQT1 and LQT2

Given the efficacy of β-blockers in LQT1, the urgency to develop alternative therapies for this form of LQTS has been scanty compared with the search for strategies to correct the loss of function caused by KCNH2 (LQT2) mutations.

Potassium Channel Openers

Using monophasic action potential recordings, Shimizu et al showed that intravenous administration of nicorandil, an IK-ATP (ATP-dependent potassium current) channel opener, reduces epinephrine-induced prolongation of the QT interval and monophasic action potential duration in LQT1 patients. Experimental data from wedge studies suggest that nicorandil (2 to 20 μmol/L) abbreviates QT interval and action potential duration, because this compound appears devoid of effects on IKr or IKs channels, and it should be considered an “aspecific” intervention to rescue repolarization incompetence in mutant myocytes cells. Unfortunately, oral administration of nicorandil reaches much lower plasma concentrations than those used in the experimental setting (0.2 to 0.3 μmol/L), thus limiting the potential for its use in the clinics; the development of nicorandil derivatives may be worthwhile.
Potassium Supplements

The evidence that conductance of KCNH2 channels is directly related to extracellular K⁺ suggested that use of potassium supplements can enhance IKr current and at least partially compensate for the loss of IKr in LQT2. In a pilot clinical study, it has been demonstrated that an increase by 1.5 mEq/L of plasma K⁺ above baseline shortens and almost normalizes previously prolonged QT intervals. The same group reported the persistence of QT shortening during chronic treatment with fexofenadine. No other electrophysiological effects. No clinical experience demonstrates that the use of potassium supplements is applicable in clinics.

Rescue of Defective Trafficking

Several strategies to rescue the defective trafficking of LQT2 mutants were explored in the last 10 years. Initially, HERG mutants were cultured at reduced temperature (27°C) or with HERG blockers (eg, E4031, cisaipride). Unfortunately, despite the ability of these compounds to restore trafficking, they also block the HERG channel at similar concentrations; therefore, it has been logical to explore the effect of other drugs in the attempt to separate the improvement of trafficking from channel blockade. Two agents were considered as particularly promising: fexofenadine, a metabolite of terfenadine, and thapsigargin. The latter compound is an inhibitor of the sarco(endo)plasmic reticulum calcium ATPase that could act through the modulation of the calcium-dependent chaperone proteins.

An innovative “molecular” approach trafficking correction was also proposed. Delisle et al tested the hypothesis that an amino acid substitution in the putative drug binding domain could compensate for protein trafficking abnormalities. In this study, the authors observed that the Y652C substitution, and to a lesser extent the Y652S substitution, counteract the trafficking defect of a LQT2 mutation (G601S). Indeed, both these substitutions increased Golgi processing of G601S channel proteins. Taken together, these studies suggest that it is possible to restore HERG protein trafficking in several ways, thus raising the interest for the development of strategies that may be applicable in clinics.

Mechanisms and Gene-Specific Therapy for LQT3

The Initial Experience

Bennet et al demonstrated that the deletion of the 3 amino acids in the cytoplasmic linker between transmembrane domains III and IV of SCN5A (commonly referred to as δ-KPQ, one of the first LQT3 mutations identified) impairs inactivation and causes late “sustained” sodium current. The increased amount of sodium entering the cell during phase 1 to 2 of cardiac action potential increases action potential duration and QT interval. Thus, LQT3 is caused by a gain of function of sodium current (INa). On this basis, the consequence of pharmacological blockade of INa was assessed in LQT3. The first clinical observation was reported in 1995 by Schwartz et al and demonstrated that mexiletine significantly shortens the QT interval in LQT3 but not in LQT2 patients. Subsequently, we reported that mexiletine can significantly shorten the APD in a cellular model mimicking the SCN5A defects (LQT3), but not in a cellular model mimicking the HERG defects (LQT2). At the same time, Wang et al demonstrated that therapeutic concentrations of mexiletine preferentially suppress the late sodium current compared with the peak, and it may rescue the defect of mutant SCN5A. As a consequence, gene-specific therapy for LQT3 with sodium channel blocking agents was broadly accepted in the clinical setting, even in the absence of a conclusive demonstration that this approach reduces mortality.

More recently, the biophysical assessment of multiple SCN5A-LQT3 mutants has revealed a spectrum of possible underlying abnormalities. Such functional heterogeneity accounts for the variable response of mutations to the administration of sodium channel blockers and explains why not all LQT3 patients benefit from treatment with these drugs. Furthermore, administration of sodium channel blockers may be detrimental when in carriers of mutations with unknown functional profile. In fact, it has been reported that SCN5A mutations may lead to some extremely complex phenotypes, such as the so-called “overlapping syndromes” (coexistence of LQT3, Brugada Syndrome, and conduction defects), and even dilated cardiomyopathy.

Is It Possible to Predict LQT3 Response to Mexiletine?

GIVEN that not all the SCN5A mutations identified in LQT3 patients respond to mexiletine, it becomes logical to attempt the identification of the critical properties that may allow to identify sensitive mutants and to select a priori the carriers who could benefit from the therapy. Starting from the notion of the need for a “mutation-targeted approach,” we attempted to identify such “critical” parameters. We selected 5 LQT3 probands with documented ventricular tachyarrhythmia before therapy who were treated with mexiletine. Over a mean follow-up of 4.6 years on mexiletine, 3 probands who responded to mexiletine with QTc shortening remained free from cardiac events. Two patients who had negligible or no QTc shortening died on cardiac arrest during mexiletine therapy. Our results suggested that a negative V1/2 shift of steady-state inactivation together with the EC50 for use-dependent block are invariably associated with good clinical response to mexiletine (Figure 4). Overall, this study shows that the mutation-specific response to sodium channel blockers is related to identifiable biophysical properties and proves the concept that in vitro analysis can identify responders versus nonresponders.

Therefore, it appears that genotype-phenotype correlation studies have outlined the “average” behavior, but the next
challenge is to characterize “mutation-specific” characteristics. Along this line, we identified a child carrier of a de novo SCN5A mutation, which causes a large sustained sodium current but also reduction of peak current density, the latter being a typical feature of Brugada syndrome. Clinically, mexiletine therapy turned out to be detrimental in this individual, as it dramatically worsened the arrhythmias. When we performed in vitro study functional characterization, we discovered that mexiletine was not only blocking the sodium current that could benefit the patient, but it also rescued the trafficking defect caused by the mutant, thus increasing the sustained sodium current. Overall, the prevailing effect of mexiletine in this subject was the paradoxical worsening of the clinical phenotype.41

LQT3-Like Phenotypes and Gene-Specific Therapy
The identification of mutations on genes that do not encode ion channels have highlighted that dysfunction in the regulatory pathways that modulate sodium current may cause LQT3. Caveolin-3 mutations have been identified in 4 of 905 LQTS probands with negative genotyping. In vitro functional characterization of mutant caveolin-3 resulted in a 2- to 3-fold increase in late INa when compared with wild type.7 A similar effect on INa was reported in association with a mutation identified in a sodium channel β-4 subunit (SCNB4) mutation found in 1 of 262 LQTS genotype-negative patients.42 Finally, in 2008, a completely novel mechanism, again eventually involving the cardiac sodium channel, was reported by Ueda et al.5 Syntrophin (SNTA1) is known to

Figure 4. ECG of LQT3 patients before and after mexiletine therapy. A, R1626P and P1332L respond to mexiletine with a QTc shortening. B, S941N and M1652R are insensitive to mexiletine with no or negligible QTc shortening. Data are from reference 40. Mex indicates mexiletine.

Figure 5. Mutations that are sensitive to mexiletine show a negative shift of steady-state inactivation curves (A) and greater use of dependent block by mexiletine (B). Data are from reference 46.
associate with the cardiac sodium channel SCN5A. One mutation was identified in a patient with a typical LQTS phenotype. A390V-SNTA1 selectively disrupted association of PMCA4b (a NOS regulator) and nNOS with SCN5A, and it increased the nitrosylation of SCN5A. A390V-SNTA1 expressed with SCN5A, nNOS, and PMCA4b in heterologous cells increased peak and late INa as compared with WT-SNTA1.

On the basis of these findings, it seems that mutation of caveolin-3, SCN4B, and SNTA1 cause LQTS by increasing INa. The paucity of genotyped patients prevents to draw any conclusion on their phenotype; clearly, if more patients with mutations in these genes are identified, it will be interesting to explore whether they shorten QT interval in response to sodium channel blockers.

Conclusions

In the past decade, the identification of genetic defects underlying LQTS has allowed to use molecular data for establishing genotype-phenotype characteristics that are now applied to risk stratification. The successful response of LQT1 patients to β-blockers clearly demonstrates the importance of selecting therapy in the context of the molecular substrate.

Several gene-specific compounds have been tested, and some have been found effective in vitro or in limited clinical studies to shorten repolarization. Whether their use can be brought to clinics and whether it will also reduce life-threatening arrhythmias remain to be established.

Although it is possible to envision that in the future LQTS therapy will include agents that specifically counteract the molecular abnormalities, a lot of work is still required to identify agents with an acceptable balance between efficacy and side effects. Meanwhile, it is important to note that the role of β-blockers remains pivotal in the management of the syndrome, and these drugs are first-line treatment for patients with clinical diagnosis.

The identification of a large number of new genes that account for a small proportion of affected patients and the evidence that multiple mechanisms may lead to similar clinical phenotypes highlight the view that a gene-specific therapeutic approach may be much more complex than previously anticipated and may not become available for all patients.

Even when we limit the scope to develop new treatments to the most prevalent genetic variants of LQTS, we have to face a challenge. Given the large number of mutations identified and their phenotypic complexity, it is clearly impossible to anticipate a scenario in which each mutation will be managed through a specific therapy; however, a balance between “one treatment fits all” and “a specific treatment for each patients” is likely to become possible. The evidence that mutations in the SCN5A gene may be clustered based on their electrophysiological profile and that the response to mexiletine may be predicted on functional basis provide a rationale template to move toward a mutation-specific therapy. It seems, therefore, reasonable to conclude that in-depth characterization of large numbers of mutations with standardized protocols may allow “functional clustering” of mutants that corresponds to clinical efficacy of specific drugs. Again, it is important to call for a thorough collaboration of basic and clinical scientists to research a “personalized treatment” for inherited arrhythmogenic diseases.

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Disclosures

None.

References


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