Review

The long QT syndrome: Therapeutic implications of a genetic diagnosis

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Abstract

The congenital long QT syndrome (LQTS) is a hereditary disorder characterized by a prolonged QT interval and a polymorphic ventricular tachycardia, known as Torsade de Pointes (TdP), leading to severe cardiac events such as syncope and/or sudden cardiac death. Molecular genetic studies have revealed a total of eight forms of congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21. Genotype–phenotype correlation in clinical and experimental studies has been investigated in detail in the LQT1, LQT2 and LQT3 syndromes which constitute more than 90% of genotyped patients with LQTS, enabling us to stratify risk and to effectively treat genotyped patients.

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1. Introduction

Over the past decade molecular genetic research has established a link between a number of inherited lethal cardiac arrhythmias and mutations in genes encoding for ion channels or other membrane components. These inherited cardiac arrhythmias include the congenital and acquired long QT syndrome (LQTS) [1,2], the Brugada syndrome [3], progressive cardiac conduction defect (Lenceg syndrome) [4], catecholaminergic polymorphic ventricular tachycardia [5,6], arrhythmogenic right ventricular cardiomyopathy [7], familial atrial fibrillation [8], the familial sick sinus syndrome [9,10] and the short QT syndrome [11]. Genotype–phenotype correlations demonstrated in clinical and experimental studies have enabled us to stratify risk and to effectively treat patients with some of the inherited cardiac arrhythmia syndromes. The congenital LQTS is a Rosetta stone for studying the genetic basis of inherited cardiac arrhythmias, in that multiple genes encoding the different ion channels or membrane adaptor have been identified, and the genotype–phenotype correlation has been rigorously investigated.

The congenital form of LQTS is characterized by a prolonged QT interval in the electrocardiogram (ECG), and a polymorphic ventricular tachycardia known as Torsade de Pointes (TdP) [12–14]. Many patients with congenital LQTS suffer from severe cardiac events such as syncope and/or sudden cardiac death, most often during physical exercise or mental stress [15]. However, cardiac events occasionally occur at rest, during sleep, or under specific circumstances with arousal. Because familial cases of LQTS have long been recognized, inheritance was suggested before molecular screening became available. Since 1995, when the first two genes responsible for LQTS were identified [16,17], molecular genetic studies have revealed a total of eight forms of congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21 [18–21]. Mutations in KCNQ1 and KCNE1, the α and β subunits of the potassium channel gene, respectively, are responsible for defects (loss of function) in the slowly activating component of the delayed rectifier potassium current (IKs) underlying the LQT1 and LQT5 forms of LQTS [22,23]. Mutations in KCNH2 and

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KCNE2 cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{K,1}) responsible for the LQT2 and LQT6 forms [16,24]. Mutations in SCN5A, the gene that encodes the α subunit of the sodium channel, result in an increase (gain of function) in the late sodium current (I_{Na}) responsible for LQT3 [17]. Mutations in KCNJ2 encoding for the inward rectifier potassium current (I_{K,1}) were found to underlie Andersen–Tawil syndrome (LQT7), in which QT prolongation and ventricular arrhythmias are accompanied by periodic paralysis and dysmorphic features [19]. Recently, a mutation in Ankyrin-B, a member of a family of versatile membrane adapters, was reported to lead to the intracellular Ca^{2+} overload which underlies the LQT4 syndrome [20]. Most recently, a mutation in CACNA1C was reported to be responsible for the defect in the L-type calcium current (I_{Ca,L}) underlying the LQT8 form, an arrhythmia disorder associated with dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism [21]. At least some cases of sudden infant death syndrome (SIDS) are attributable to congenital LQTS [25], in which SCN5A mutations are reported [26,27]. In all genetic forms, decreases in outward potassium currents (I_{Ks}, I_{Kr}, I_{K1}) or increases in inward sodium or calcium current (late I_{Na}, I_{Ca,L}) prolong the action potential duration (APD), resulting in prolongation of the QT interval, a common phenotype in LQTS. However, responsible mutations can be identified among the 8 genes in only 50–70% of clinically affected probands, whereas the remaining 30–50% of probands cannot be genotyped. Of the 8 forms, the LQT1 and LQT2 syndromes are the two commonest genetic variants, and each accounts for approximately 40% of genotyped patients [18]. The LQT3 syndrome accounts for approximately 10% of genotyped patients [18]. Since the LQT1, LQT2 and LQT3 forms constitute more than 90% of genotyped patients with LQTS [18], the genotype–phenotype correlation has been investigated in detail in the LQT1, LQT2 and LQT3 syndromes.

2. Electrocardiographic characteristics

A greatly advanced knowledge of the cellular basis for the T wave in the ECG is attributed to experimental studies using arterially perfused canine ventricular wedge preparations, in which transmembrane action potentials from epicardial, mid-myocardial and endocardial cells are simultaneously recorded, together with a pseudo-ECG along the same axis [28–31]. The electrical currents which flow down voltage gradients on either side of the mid-myocardial region across the ventricular wall are believed to determine the morphology and duration of the T wave in the ECG, at least in the unipolar left precordial leads (V4–V6) which reflect the potentials of the left ventricular free wall. Under normal conditions, repolarization of the epicardial action potential occurs first, and coincides with the peak of the normal T wave, while repolarization of the longest action potential in the mid-myocardial layer coincides with the end of the T wave. Repolarization of the endocardial cells usually occurs between repolarization of the epicardial and the mid-myocardial cells. Because the action potential plateau consists of the sum of several ionic currents, differential modification of the ionic currents in each cell type by mutations in each LQTS gene is expected to result in a variety of QT interval and T wave morphologies.

Broad-based prolonged T waves are more commonly observed in the LQT1 syndrome, whereas low-amplitude T waves with a notched or bifurcated configuration are seen more frequently in the LQT2 syndrome [32]. LQT3 patients often show late-appearing T waves with a prolonged isoelectric ST-segment [32]. However, exceptions are present in all 3 genotypes [33], and the T wave pattern varies with time, even in the same patient with a specific mutation. The characteristic T wave morphology is reportedly revealed by exercise treadmill testing or catecholamine infusion in patients with LQT1 and LQT2 syndromes [34]. No specific T wave pattern has been suggested in the LQT5 and LQT6 syndromes. TU abnormalities such as biphasic T waves following long pauses like those found in the LQT2 syndrome are commonly observed in the LQT4 syndrome [20]. Enlarged U waves separated from the T wave, and frequent ventricular premature contractions are reported to be characteristic ECG features in the LQT7 syndrome [19]. Pharmacological LQTS models employing arterially perfused wedges have demonstrated that the differential time course of repolarization in the epicardial, mid-myocardial and endocardial cells as a result of mutations in each gene is responsible for the characteristic T wave morphologies in the LQT1, LQT2, LQT3 syndromes and probably in other genotypes [35–39].

3. Optimal management based on genotype–phenotype correlation

Previous clinical studies on genotype–phenotype correlation have reported differential triggers for cardiac events, clinical course and risk stratification between each genotype, especially in the LQT1, LQT2 and LQT3 syndromes.

3.1. Genotype-specific triggers for cardiac events

Clinical evidence has suggested genotype-specific triggers for cardiac events in patients with the LQT1, LQT2 and LQT3 syndromes [40–44]. Schwartz et al. analyzed data from the International LQTS Registry and reported that cardiac events most frequently occur during exercise (62%) but only rarely during sleep and rest (3%) in LQT1 patients [40,42]. Swimming is a common trigger in the LQT1 syndrome [41,43]. In contrast to the pattern shown in LQT1 patients, cardiac events principally occur during sleep and rest (39%), and exercise-related cardiac events are rare
(13%) in LQT3 patients [40]. In LQT2 patients, cardiac events occur equally during exercise (13%) or during sleep/rest (15%) [40]. More importantly, a sudden startle in the form of an auditory stimulus (a telephone, alarm clock, ambulance siren, etc.) is a specific trigger in the LQT2 syndrome [41,42]. Although the LQTS women are generally susceptible to cardiac events during postpartum periods, the LQT2 women have recently been reported to be most susceptible [44]. Exercise or mental stress often trigger ventricular arrhythmias in LQT4 patients [20]. In LQT7 patients, hypokalemia is often associated with frequent ventricular arrhythmias as well as periodic paralysis [19]. Information on genotype-specific triggers can enable physicians to take care of their LQTS patients more effectively. Exercise should be limited more strictly in LQT1 patients, in particular swimming or diving. LQT2 patients should be advised to avoid noises such as alarm clocks and telephones.

The experimental study by Priori et al. using guinea pig ventricular myocytes suggested for the first time that the genotype-specific triggers for cardiac events are a result of a differential response of ventricular repolarization to sympathetic stimulation between each genotype [45]. They demonstrated that the APD of cells pretreated with anthopleurin (LQT3 model) was shortened by β-adrenergic stimulation with isoproterenol, whereas the APD of cells exposed to dofetilide (LQT2 model) was even prolonged initially in response to isoproterenol. The increased sensitivity of LQT1 to sympathetic stimulation can be explained by the fact that genetically impaired $I_{Ks}$ is unable to adequately shorten APD during sympathetic stimulation [46].

Experimental studies employing arterially perfused wedge preparations further advanced our knowledge on the mechanism of the genotype-specific triggers for cardiac events. The data suggest a genotype-specific response of the APD and the transmural dispersion of repolarization (TDR), defined as the difference between the maximum and the minimum APD across the ventricular wall, to isoproterenol in the LQT1, LQT2 and LQT3 models [35,38]. In the LQT1 model, isoproterenol prolongs the QT interval and the APD of the mid-myocardial cells, but abbreviates epicardial and endocardial APD, resulting in a persistent increase in the QT interval and the TDR, which may explain the greater sensitivity of LQT1 patients to sympathetic stimulation [38]. In the LQT2 model, isoproterenol initially prolongs and then abbreviates the QT interval and the mid-myocardial APD to the baseline level, whereas the epicardial and endocardial APD is always abbreviated, leading to a transient increase in the QT interval and the TDR, consistent with the nature of TdP, which is often observed following a startle [38]. In the LQT3 model, isoproterenol produces a persistent abbreviation of the QT interval and the APD of the all cell types, resulting in a persistent decrease of the QT interval and TDR, which may explain why cardiac events occur more frequently during sleep and rest when sympathetic tone is low in LQT3 patients [38].

### 3.2. Usefulness of provocative testing

The differential responses of ventricular repolarization to sympathetic stimulation between each genotype have also been investigated in clinical studies [34,47–52]. Clinical data using epinephrine infusion or treadmill exercise testing suggested that sympathetic stimulation produces genotype-specific responses of the QT interval and the Tpeak–Tend interval reflecting TDR in LQT1, LQT2 and LQT3 patients (Fig. 1A). Epinephrine remarkably prolongs the corrected QT (QTc) interval at peak effect when the heart rate is increased. The experimental study by Priori et al. using guinea pig ventricular myocytes suggested for the first time that the genotype-specific triggers for cardiac events are a result of a differential response of ventricular repolarization to sympathetic stimulation between each genotype [45]. They demonstrated that the APD of cells pretreated with anthopleurin (LQT3 model) was shortened by β-adrenergic stimulation with isoproterenol, whereas the APD of cells exposed to dofetilide (LQT2 model) was even prolonged initially in response to isoproterenol. The increased sensitivity of LQT1 to sympathetic stimulation can be explained by the fact that genetically impaired $I_{Ks}$ is unable to adequately shorten APD during sympathetic stimulation [46].

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maximally increased (1–2 min after the start of epinephrine), and the QTc remains prolonged during steady-state epinephrine effect (3–5 min after the start of epinephrine) in LQT1 patients [48,51,52]. The QTc interval is also prolonged at peak epinephrine effect in LQT2 patients, but returns to close to the baseline levels at steady state epinephrine effect [48,52]. In contrast, the QTc is less prolonged at peak epinephrine effect in LQT3 patients than in LQT1 or LQT2 patients, and is abbreviated below the baseline levels at steady state epinephrine effect [48,52]. The response of the Tpeak–Tend interval approximately parallels that of the QT interval [47,50], supporting the cellular basis for genotype-specific triggers for cardiac events.

Epinephrine challenge is reported to establish an ECG diagnosis in silent mutation carriers of LQTS, especially the LQT1 genotype [51,52]. Epinephrine infusion is also useful to predict the genotype of the LQT1, LQT2 and LQT3 syndromes by the specific response of the QT interval (Fig. 1B) [52].

3.3. Genotype-specific clinical course

LQT1 and LQT2 patients show a higher frequency and cumulative probability of cardiac events than LQT3 patients [53]. However, the lethality of the cardiac events is higher in LQT3 patients. Male patients are generally younger than female patients at first cardiac events [54]. It is noteworthy that many first cardiac events occur before the age of 15 in male patients, particularly in LQT1 males, whereas female patients may experience first cardiac events after the age of 20 [54]. These data suggest that LQT1 males require stricter exercise restriction before the age of 15, but less restriction after age 15. More recently, risk stratification according to age, gender and QTc interval has been recommended [55]. For example, LQT1 and LQT2 patients and only LQT3 males who have a QTc interval of ≥500 ms are categorized as high risk groups—however, exceptions exist, and we must be very careful to advise each patient on a case-by-case basis.

4. Genotype-specific treatment based on clinical and experimental data

It has been empirically believed that β-blockers and strict exercise restriction are the most effective therapy for patients with congenital LQTS [56]. However, β-blockers are known not to be protective in all patients. A direct link between mutations in the ion channel genes and each genotype has made possible the advent of genotype-specific treatments for each LQTS genotype. In 1995, Schwartz and co-workers first reported the possibility of genotype-specific treatment. They demonstrated that sodium channel block with mexiletine or rapid heart rate is much more effective in abbreviating the QT interval in LQT3 patients than in LQT2 patients [57]. Preliminary clinical studies have since suggested the feasibility of genotype-specific therapy based on abbreviations of the QT interval by therapeutic agents or other interventions in each genotype [40,58]. However, the ability to abbreviate the QT interval by these interventions does not necessarily reflect their efficacy in reducing arrhythmic risk or sudden cardiac death. The experimental studies by pharmacological LQTS models using wedge preparations have provided a quantitative assessment of genotype-specific treatments for each LQTS genotype (Table 1) [28,35–39].

4.1. LQT1

4.1.1. β-Blockers

β-Blockers have long been the first choice of therapy in patients with congenital LQTS before molecular screening was available [56]. Clinical data from the International Registry of LQTS reported that β-blockers more frequently suppress an episode of syncope and sudden cardiac death in LQT1 patients (81%) than in LQT2 (59%) or LQT3 (50%) patients [40]. Priori et al. also studied the outcomes during β-blocker therapy for Italian LQTS patients, and found the same results [59]. Experimental data suggested that propranolol, a β-blocker, completely suppresses the effect of isoproterenol to persistently increase TDR and to induce TdP in the LQT1 model, supporting the genotype-specific efficacy of β-blockers in the LQT1 syndrome [35,38].

4.1.2. IB sodium channel blocker (mexiletine)

Although it is reported that mexiletine, a class IB sodium channel blocker which blocks late \( I_{Na} \), abbreviates the QT interval dramatically in LQT3 patients [57], experimental data from wedge studies suggested that mexiletine reduces

| Genotype-specific therapy based on clinical and experimental data in long QT Syndrome |
|---------------------------------------------|---------------|--------------|
| LQT1 (LQT5) | LQT2 (LQT6) | LQT3 |
| Sensitivity to sympathetic stimulation (Sustained ↑ in TDR) | ++++ | ++ (Transient ↑ in TDR) | – (↓ in TDR) |
| Torsade de Pointes Specific trigger | Exercise-related Swimming | Startle Telephone, Alarm clock, Postpartum periods | Sleep/Rest |
| Exercise restriction | ++++ | ++ | – |
| β-Blockers | ++++ | ++ | – |
| Potassium supply | ++ | +++ | ++ |
| Class IB sodium channel blockers | +++ | +++ | ++++ |
| Calcium channel blockers | +++ | ++ | ++ |
| Potassium channel blockers | ++ | ++ | – |
| Pacemaker | ++ | ++ | ++++ |
| ICD | ++++ | ++++ | ++++ |

ICD, implantable cardioverter-defibrillator; TDR, transmural dispersion of repolarization. ++++ means most effective. a Based only on experimental data.
TDR and suppresses the development of TdP equally in the LQT1, LQT2 and LQT3 models [28,35]. This is mainly due to the intrinsically larger late \( I_{Na} \) in mid-myocardial cells than in epicardial or endocardial cells [60]. Therefore, mexiletine may at least warrant consideration as conjunctive therapy in addition to \( \beta \)-blockers in LQT1 patients.

4.1.3. Other pharmacological agents

We previously used monophasic action potential (MAP) recordings and reported that verapamil, an \( I_{Ca-L} \) blocker, shortens the QT and MAP duration and suppresses epinephrine-induced early afterdepolarizations (EADs) in congenital LQTS patients, most of whom were diagnosed later as having the LQT1 or LQT2 syndrome [61]. Recent experimental studies also suggested the effectiveness of verapamil in decreasing the QT interval and TDR and abolishing EADs and TdP in a combination of congenital and acquired LQTS (LQT1+LQT2) [62]. Because verapamil is also a potent inhibitor of late \( I_{Na} \), like many other calcium channel blockers, verapamil may also be suitable for conjunctive therapy.

Nicorandil, an \( I_{K-ATP} \) opener, is clinically available in Japan and in some European countries. Clinical studies using MAP recordings demonstrated that intravenous administration of nicorandil reverses epinephrine-induced QT and MAP prolongation and suppresses epinephrine-induced EADs in LQT1 patients [63]. Our experimental study also suggested that relatively high concentrations (10–20 \( \mu \)mol/L) of nicorandil completely reverse the effects of chromanol 293B+isoproterenol and of D-sotalol to increase APD and TDR, and to induce TdP in the LQT1 and LQT2 models [39]. With regard to the therapeutic concentration of nicorandil, intravenous nicorandil might be of therapeutic value in suppressing repetitive episodes of TdP in the LQT1 and LQT2 patients, but not oral nicorandil.

It is noteworthy that prospective clinical data of the effectiveness of verapamil or nicorandil is lacking. Moreover, the series of LQTS treated with therapies other than \( \beta \)-blockers reported in the earlier studies showed unsatisfactory results [64]. Therefore, we will have to wait for prospective clinical trials to apply new strategies to LQTS patients.

4.1.4. Pacemakers

Previous MAP studies showed that atrial pacing not associated with sympathetic stimulation shortens the QT interval and MAP duration more significantly in LQTS patients (mostly LQT1 or LQT2) than in controls [65]. Moreover, experimental data from wedge studies showed that the APD-, QT- and TDR-rate relationships are much steeper in the LQT3 model than in the LQT1 or LQT2 models, but the relationships in the LQT1 and LQT2 models are still steeper than under control conditions [28,35], suggesting that pacemaker therapy may also be useful even in LQT1 patients, specifically those with bradycardia. The efficacy of combined use of \( \beta \)-blockers and long-term pacing therapy for patients with LQTS has been reported [66].

4.1.5. Left cardiac sympathetic denervation

The efficacy of left cardiac sympathetic denervation (LCSD) has been reported in LQTS patients, especially those who are refractory to \( \beta \)-blocker therapy [67,68]. Since LQT1 patients are most sensitive to sympathetic stimulation, LCSD is expected to be most effective in the LQT1 syndrome [68].

4.1.6. Implantable cardioverter-defibrillator

An implantable cardioverter-defibrillator (ICD) is indicated for LQTS patients who have suffered an aborted cardiac arrest and/or who have repetitive episodes of syncope in the presence of pharmacological and non-pharmacological therapy, regardless of genotype [69,70].

4.2. LQT2

4.2.1. \( \beta \)-Blockers

A \( \beta \)-blocker is the first choice of pharmacological therapy in LQT2 patients [40], however the recurrence rate is higher than that in LQT1 patients. Therefore, conjunctive pharmacological therapy with mexiletine and/or verapamil in addition to \( \beta \)-blockers is more frequently required in LQT2 patients.

4.2.2. Potassium supply

As the \( I_{Kr} \) defect is responsible for the LQT2 syndrome and \( I_{Kr} \) is sensitive to extracellular potassium level, serum potassium level is expected to play a key role in LQT2 patients. Experimental wedge studies suggested that an increase in extracellular potassium can limit the development of an arrhythmogenic substrate under long QT conditions, due principally to its action to increase \( I_{K1} \), \( I_{K} \) and limit the potency of \( I_{K} \), blockers [29]. In clinical practice, exogenously administered potassium was reported to correct repolarization abnormalities in LQT2 patients with \( I_{Kr} \) defects [71]. Long-term oral potassium administration was recently shown to improve repolarization abnormalities in LQT2 patients [72]. Acute intravenous treatment with potassium is especially effective in suppressing TdP [73].

4.2.3. Pharmacological rescue

Albeit still at the experimental level, several agents, which block \( I_{Kr} \) current, were reported to rescue defective protein- trafficking of the KCNH2 mutations [74]. This pharmacological rescue may represent a new antiarrhythmic paradigm in the treatment of some trafficking-defective LQT2 mutations.

4.2.4. Pacemakers

Pause-dependent QT prolongation and a “short–long–short” initiating sequence of TdP are commonly observed in some patients with congenital as well as acquired LQTS [75]. Recently, pause-dependent TdP is reported to be more frequently recognized in LQT2 patients than in the other forms [76]. Therefore, constant pacing with pacemaker
therapy may be of therapeutic value in preventing TdP by suppressing pause in LQT2 patients.

4.2.5. Implantable cardioverter-defibrillator

The indication of the ICD is similar as that in the LQT1 syndrome.

4.3. LQT3

4.3.1. β-Blockers

Clinical data from the International LQTS Registry suggested that β-blockers are less effective in LQT3 patients than in LQT1 or LQT2 patients [40]. In experimental LQT3 models, sympathetic stimulation with isoproterenol persistently decreases TDR and suppresses TdP, and propranolol, a β-blocker, antagonizes the protective effects of isoproterenol [38], indicating that β-blockers are not protective or may even be harmful in LQT3 patients.

4.3.2. IB sodium channel blockers (mexiletine, flecainide)

Both preliminary clinical data and the experimental data employing wedge preparations suggested that mexiletine, a class IB sodium channel blocker, is more effective in abbreviating the QT interval in the LQT3 syndrome than in the LQT1 or LQT2 syndrome (Fig. 2B) [28,35,57]. These data encourage us to use mexiletine as a first line of therapy in LQT3 patients. However, an LQT3 patient, who was refractory to mexiletine, has recently reported [77]. At the moment, mexiletine should be used in the presence of β-blockers or with the backup of an ICD even in LQT3 patients until prospective clinical trials confirm the effectiveness of mexiletine.

Benhorin and co-workers reported the effectiveness of flecainide, a class IC sodium channel blocker, in abbreviating the QT interval in LQT3 patients with a specific mutation (D1790G) in SCN5A [78]. However, flecainide is reported to elicit a Brugada phenotype in some of LQT3 patients (Fig. 2C) [79]. Therefore, flecainide should not be used in LQT3 patients, except for those with this specific SCN5A mutation.

4.3.3. Pacemakers

Schwartz et al. indicated the specific efficacy of pacemaker therapy in LQT3 patients, because an increase of heart rate with exercise abbreviated the QT interval more effectively in LQT3 patients than in LQT2 patients [57]. The APD-, QT- and TDR-rate relationships in the experimental studies also supported the specific efficacy of pacing in the LQT3 syndrome, possibly due to slow kinetics of reactivation of late I\textsubscript{Na} in this genotype [28,35].

4.3.4. Implantable cardioverter-defibrillator

As the lethality of the cardiac events is reported to be higher in LQT3 patients than in either LQT1 or LQT2 patients [53], an ICD implantation may be encouraged more aggressively in patients with LQT3 syndrome who experience an aborted cardiac arrest than patients with LQT1 or LQT2.

Fig. 2. Effects of sodium channel blockers, mexiletine and flecainide, in a patient with the LQT3 form of congenital long QT syndrome. A: The corrected QT (QTc) interval is prolonged (572 ms) under control conditions. B: Injection of mexiletine (125 mg), a class IB sodium channel blocker, normalizes the QTc to 433 ms. C: Injection of flecainide (100 mg), a class IC sodium channel blocker, also dramatically abbreviates the QTc to 465 ms, but unveils Brugada-like ST-segment elevation in lead V2.
4.4. LQT4 to LQT8

Genotype-specific management and treatment are unknown in the other forms, LQT4 to LQT8, because of the very small number of patients. β-Blockers are recommended in general, but an ICD should be considered to implant in patients with an aborted cardiac arrest and/or repetitive episodes of syncope refractory to β-blockers. Mutations in KCNE1 and KCNE2 in the LQT5 and LQT6 syndromes are responsible for defects of $I_{Ks}$ and $I_{Kr}$ respectively [22,23], therefore, therapy for LQT1 and LQT2 patients may be applied in LQT5 and LQT6 patients respectively.

4.5. Genotype-unknown LQTS

A β-blocker is the first line of therapy in patients with genotype-unknown LQTS, who account for 30–50% of clinically diagnosed LQTS patients. It is of importance to diagnose which form of the LQTS the patients are affected with on the basis of clinical test, such as epinephrine test. The genotype prediction by epinephrine test may help to stratify the treatment of patients, if the patients are not genotyped by the molecular screening.

5. Possibility of mutation site-specific management and therapy

To date, more than 300 distinct mutations involving the 8 LQTS genes have been reported, mainly in the LQT1, LQT2 and LQT3 genes. The structure of each cardiac ion channel or the correspondence between the mutation site...
and the channel function has been clearly disclosed. Therefore, mutation site-specific differences in severity of clinical phenotype or responses to therapy could be expected. In 2002, Moss and co-workers suggested that LQT2 patients with mutations in the pore region of the KCNH2 gene are at markedly increased risk of arrhythmia-related cardiac events compared with patients with non-pore mutations in the International LQTS Registry [80]. Regarding the LQT1 syndrome, Zareba et al. found no significant differences in the QTc interval or the risk of cardiac events based on the mutation location in the KCNQ1 gene [81]. Donger et al. had previously suggested that the specific missense mutation (R555C) located in the C-terminal region of the KCNQ1 gene was associated with a less severe phenotype than the mutations in the transmembrane regions [2]. We recently compared the arrhythmic risk and sensitivity to sympathetic stimulation with treadmill exercise testing between Japanese LQT1 patients with transmembrane mutations and those with C-terminal mutations in the KCNQ1 gene [82]. Our data suggested that patients with transmembrane mutations have a longer QTc and corrected Tpeak–Tend interval and more frequent LQTS-related cardiac events than those with C-terminal mutations (Fig. 3) [82]. Moreover, the QTc and corrected Tpeak–Tend were more prominently increased with exercise in patients with transmembrane mutations (Fig. 4) [82].

Our data in LQT1 as well as data by Moss et al. in LQT2 indicate the possibility of mutation site-specific management or treatment in each genotype. However, a tremendous clinical variability in a family with a specific mutation is often recognized. Therefore, a larger patient population is needed to make a definitive conclusion about the mutation site-specific differences in clinical phenotype.

6. Ethnicity and common polymorphisms

The discrepancy between our Japanese population and the population from the International Registry in mutation site-specific differences in clinical phenotype in the LQT1 syndrome may be in part attributable to ethnicity-specific common polymorphisms. Common polymorphisms in the ion channel gene is usually functionally silent — the functional phenotype associated with polymorphism channels is usually indistinguishable from the functional phenotype associated with wild-type channels. However, Splawiaki et al. suggested that a predominantly Negroid-specific common polymorphism, S1103Y in the SCN5A gene, is associated with arrhythmia risk [83], supporting the concept that common genetic determinants may mediate arrhythmia susceptibility. An Asian-specific common polymorphism, G643S in the KCNQ1 gene, has been shown to have a subtle functional LQTS-phenotype in vitro [84]. The prevalence of G643S is reported to be approximately 11% in the Japanese population, and of the 15 patients with G643S for our Japanese cohort were brought to medical attention as an acquired form of LQTS associated with class IA antiarrhythmic agent and/or bradycardia (unpublished data). These data suggest that ethnicity-specific common polymorphisms can mediate genetic susceptibility for arrhythmia risk as well as modify clinical phenotype caused by a responsible mutation in the LQTS gene. Further systematic and comprehensive study on common polymorphisms is required to further advance the management and treatment of patients with LQTS.

7. Summary

Recent advances in molecular genetic studies have identified a total of eight forms of congenital LQTS caused by mutations in genes of the ion channels or membrane adapter. The direct link between mutations in the ion channel or membrane adapter genes and each LQTS genotype by genotype—phenotype correlation has made possible the advent of genotype-specific management and treatment for each LQTS genotype. Further prospective and comprehensive study on genotype—mutation—phenotype correlation is needed to further advance the effective management and treatment of patients with congenital LQTS.

References


