Genotype-Phenotype Correlation in the Long-QT Syndrome
Gene-Specific Triggers for Life-Threatening Arrhythmias

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Background—The congenital long-QT syndrome (LQTS) is caused by mutations on several genes, all of which encode cardiac ion channels. The progressive understanding of the electrophysiological consequences of these mutations opens unforeseen possibilities for genotype-phenotype correlation studies. Preliminary observations suggested that the conditions (“triggers”) associated with cardiac events may in large part be gene specific.

Methods and Results—We identified 670 LQTS patients of known genotype (LQT1, n = 371; LQT2, n = 234; LQT3, n = 65) who had symptoms (syncope, cardiac arrest, sudden death) and examined whether 3 specific triggers (exercise, emotion, and sleep/rest without arousal) differed according to genotype. LQT1 patients experienced the majority of their events (62%) during exercise, and only 3% occurred during rest/sleep. These percentages were almost reversed among LQT2 and LQT3 patients, who were less likely to have events during exercise (13%) and more likely to have events during rest/sleep (29% and 39%). Lethal and nonlethal events followed the same pattern. Corrected QT interval did not differ among LQT1, LQT2, and LQT3 patients (498, 497, and 506 ms, respectively). The percent of patients who were free of recurrence with β-blocker therapy was higher and the death rate was lower among LQT1 patients (81% and 4%, respectively) than among LQT2 (59% and 4%, respectively) and LQT3 (50% and 17%, respectively) patients.

Conclusions—Life-threatening arrhythmias in LQTS patients tend to occur under specific circumstances in a gene-specific manner. These data allow new insights into the mechanisms that regulate the electrophysiological consequences of mutations on specific genes to clinical manifestations and offer the possibility of complementing traditional therapy with gene-specific approaches. (Circulation. 2001;103:89-95.)

Key Words: death, sudden ■ genetics ■ ion channels ■ long-QT syndrome ■ nervous system, autonomic

The identification between 1995 and 19961,2 of 3 of the genes responsible for the congenital long-QT syndrome (LQTS)3–6 and the realization that they all encode ion channels involved in the control of repolarization1,2 fostered the concept that LQTS may represent a unique model for the study of genotype-phenotype correlation in hereditary arrhythmogenic disorders. Interest in this correlation has been further stimulated by the demonstration that the mutations identified in these genes produce either gain or loss of function, resulting in an excess of late inward sodium current or in reduced outward potassium current.1,2 These ionic alterations...
lengthen action potential duration and explain the prolonged QT interval characteristic of LQTS.

Within months of the identification of the first 2 LQTS genes, HERG and SCN5A, some of the present authors reported gene-specific differential degrees of QT interval shortening in response to Na\(^+\) channel blockade and to heart rate increases. We also noted a seemingly different pattern in the conditions associated with syncpe and cardiac arrest. Specifically, although 6 of 7 LQT3 patients (those with mutations in SCN5A, the cardiac Na\(^+\) channel gene) experienced their cardiac events at rest or during sleep, all 5 LQT2 patients (those with mutations in HERG, the gene that encodes the rapid component of the delayed rectifier potassium current \(I_{Kr}\)) experienced their events during emotion or exercise. If confirmed, this finding might have implications for the management of LQTS patients of known genotype.

We warned against making extrapolations from such a small study and committed ourselves to test this intriguing observation in a population of symptomatic patients of known genotype that was sufficiently large to allow safe and definitive conclusions. This commitment constitutes the focus of the present study.

The identification in 1996 of \(KvLQT1\), a \(K^+\) channel gene that, when coexpressed with \(minK\), produces the slow component of the delayed rectifier potassium current \(I_{Kr}\), allowed us to extend the comparison to LQT1, the LQTS subtype with mutations on \(KvLQT1\). Here, we report the analysis of the triggers involved in the precipitation of major cardiac events in 670 LQTS patients, all symptomatic and of known genotype, who are of the LQT1, LQT2, and LQT3 subtypes.

**Methods**

For the present study, we (1) identified patients of known genotype, (2) selected among them those who experienced major cardiac events, and (3) further selected the patients whose cardiac events had been associated with, or triggered by, well-defined conditions. Patients who were of known genotype but were asymptomatic were not considered for inclusion into the study. Because the same electrophysiological mechanism, torsade de pointes (TdP), of varying duration underlies the tachyarrhythmias of LQTS and because all these tachyarrhythmias have a life-threatening potential, we did not distinguish among syncpe, cardiac arrest, or sudden cardiac death in the main analysis. However, we also separately analyzed the lethal events. Data were collected on specifically prepared forms. Whenever possible, direct contacts were established to verify the information; special care was taken for patients with multiple events, and in large part, we followed procedures that have been previously described.

The LQTS International Registry contributed 50% of the patients, and 50% originated mostly from the BIOMED LQTS Research Group but also from individual physicians.

We identified 670 patients of the LQT1, LQT2, and LQT3 subtypes; 418 (62%) had been directly genotyped. The remaining 252 (38%) patients had their genotype attributed with certainty because (1) they were obligate gene carriers or (2) they fulfilled both the rigorous criteria (score \(\geq 4\)) for definitive clinical diagnosis of LQTS\(^{10}\) and were first- or second-degree relatives of genotyped patients. The few available LQT5 and LQT6 patients were not included.

**Triggers: Definitions and Rationale**

For purposes of analysis, we identified 3 distinct conditions, or triggers, associated with the onset of cardiac events: exercise, emotion, and rest or sleep without arousal. The choice of these “classified” triggers was based on the following pathophysiological considerations.

Physical stress, or exercise, is a clear-cut condition without possibility of misinterpretation. It is either witnessed or narrated by the patient. It represents a condition associated with progressively increasing heart rate and with the release of both neural and circulating catecholamines.

The opposite condition is represented by events that occurred during sleep or rest in the presumed absence of any known arousal. This can be established for the survivors, whereas for patients found dead in bed, it is impossible to rule out an arousal before sudden death. However, sleep is not a uniformly quiet state, because periods of REM sleep are associated with abrupt increases in sympathetic activity. Events at rest were included only when the absence of a known arousal was combined with a truly resting condition (eg, lying in bed awake or in an armchair), with the exclusion of television watching, driving, and sitting in school. These events usually occur at relatively long cardiac cycles and with a modest amount of circulating catecholamines.

Between these 2 extremes, we introduced emotional stress, that is, stressful events and arousals that occur during normal daily activities (fear, anger) and arousals that occur at rest or during sleep (sudden noise, startle). This condition is usually characterized by an abrupt neurally mediated release of norepinephrine that occurs while the heart rate is relatively low and without allowance of time for QT adaptation to faster rates.

Several patients (22%) had 2 classified triggers (eg, during exercise and during emotions), and only 2 (0.4%) had 3 triggers. To avoid selection bias, where there were multiple trigger mechanisms, each of the separate triggers was included in the analysis. Sometimes the triggers were unknown or “other” (ie, outside the 3 main conditions), such as during anesthesia, fever, menses, or pregnancy-related events.

The possibilities that lethal events (sudden death and documented cardiac arrest) might differ from syncpe in their gene-specific relation to triggers and that the sex effect on the time of occurrence of the first event\(^{11}\) might differ between genotypes were considered. The sex analysis included all patients and all triggers, including those different from the classified ones.

**Response to Therapy**

The relation observed between genotype and specific triggers also suggested that the response to \(\beta\)-blockers might be in part genotype specific.

Data on therapy were available for 494 patients (74%), which also includes patients who received no treatment (in large part representing the sudden deaths that occurred before diagnosis). The treatment modality used for most patients (n=300) was \(\beta\)-blockers, and we limited our analysis to those patients (n=271, 90%) for whom precise information was available regarding both therapy and outcome. Patients were not included in this analysis if the dosage of \(\beta\)-blockers was \(\leq 0.5 \text{mg/kg/d}^{11}\) (n=2) and if therapy had been discontinued for >1 month. We also excluded 2 patients with cardiac arrest in association with a QT-prolonging drug and with non-LQTS-related surgery.

**Statistical Analysis**

A comparison among the patients of ECG variables was performed using the \(t\) test for independent samples and ANOVA with Bonferroni’s correction for multiple comparisons. Differences in other clinical features were assessed by the \(\chi^2\) method and Fisher’s exact test for dichotomous variables. Survival curves that represent cumulative event rates were obtained by using the Kaplan-Meier life-tables and were compared by the log-rank test. Data are given as mean±1 SD, and differences were accepted as significant for \(P<0.05\).

**Results**

We determined the genotype of 670 symptomatic LQTS patients (Table 1). Table 2 shows the number of patients with...
unknown trigger, with ≥1 of the 3 classified triggers, and with other nonclassifiable triggers. In 200 cases (30%), it was either not possible to identify with certainty the trigger involved (n=116) or the trigger differed from the 3 main categories chosen for analysis (n=84). Cardiac events were induced by 2 different triggers in only 10% of LQT3 patients compared with 25% of LQT1 patients \( (P=0.04) \) and 20% of LQT2 patients (NS). Of clinical relevance, among the 105 patients with 2 triggers, only 2 (2%) had events in “opposite” conditions (ie, exercise and sleep/rest without arousal).

There was no difference between the triggers for the genotyped patients and for the obligate gene carriers whose genotype had not been documented.

### Triggers and Cardiac Events

Figure 1 shows the relation among the 3 subgroups, the 3 classified triggers, and other triggers. The pattern for LQT1 is very distinctive, with most events (62%) occurring during exercise and only a very small minority (3%) occurring during rest/sleep. This is in sharp contrast with the pattern shown by LQT3 patients, for whom only 13% of the events occurred during exercise and 39% occurred at sleep/rest. LQT2 patients have an intermediate pattern, with only 13% occurring during exercise and most of the remainder (43%) occurring with emotional stress.

The frequency of lethal events (cardiac arrest and sudden death) was affected by the genotype; the rate increased from 28% for LQT1 to 40% for LQT2 to 49% for LQT3 patients. This high mortality rate depends on the noninclusion of asymptomatic patients.

The pattern observed for lethal events was similar to that for all events (ie, including syncope), but it did accentuate the differences between LQT1 versus LQT2 and LQT3. Figure 2 shows that 68% of lethal events occurred during exercise for LQT1, whereas this never occurred for LQT2 and occurred in only 4% of cases for LQT3 patients. By contrast, 49% and 64% of lethal events occurred during rest/sleep without arousal for LQT2 and LQT3 patients, respectively, whereas this occurred in only 9% of cases for LQT1 patients.

### Specific Triggers

Auditory stimuli were rare (2%) among LQT1 patients and relatively frequent (26%) among LQT2 \( (P<0.001) \). They also occurred in LQT3 (7%) less frequently than in LQT2 \( (P=0.002) \) but more frequently than in LQT1 \( (P=0.07) \) (Table 3). Conversely, 80% of the patients with events that occurred after auditory stimuli were LQT2 patients. Of note, in LQT2 patients, most of these events (64%) occurred during sleep.

Swimming, as a trigger, was particularly frequent among LQT1 patients; it occurred in 33% of patients with a known trigger (107 of 320). By contrast, it was exceptionally rare (1 of 176, 0.6%) among LQT2 patients and absent among LQT3 patients. Of the patients who experienced cardiac events while swimming, 99% were of LQT1 (Table 3).

### Corrected QT Duration and Triggers

Corrected QT (QTc) measurements were available for 517 (77%) patients (Figure 3). The 3 subgroups have very similar average values; furthermore, LQT1 and LQT2, but not LQT3, female patients have longer durations.

### Time to First Event and Genotype

For 626 patients (93%), we knew the exact age at which the first cardiac event occurred. This allowed to generate curves that show the time interval from birth to the first major cardiac event for the 3 subgroups (Figure 4). LQT1 patients were the earliest to have symptoms: 54% of them become symptomatic before age 10. By contrast, 50% of LQT2 and LQT3 patients were still asymptomatic at age 16. Figure 4

### Table 1. Demographics

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients, n</th>
<th>Families, n</th>
<th>Sex, %</th>
<th>Age, Mean±1SD y</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>371</td>
<td>97</td>
<td>56</td>
<td>35±21</td>
</tr>
<tr>
<td>LQT2</td>
<td>234</td>
<td>86</td>
<td>68</td>
<td>35±18</td>
</tr>
<tr>
<td>LQT3</td>
<td>65</td>
<td>21</td>
<td>58</td>
<td>30±19</td>
</tr>
</tbody>
</table>

### Table 2. Genotype, Patients, and Triggers

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. of Patients</th>
<th>Patients With Nonclassified Triggers, n (%)</th>
<th>Patients With Classified Triggers, n (%)</th>
<th>Total No. of Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
<td>Other</td>
<td>1 Trigger</td>
</tr>
<tr>
<td>LQT1</td>
<td>371</td>
<td>51 (14)</td>
<td>34 (9)</td>
<td>214 (75)</td>
</tr>
<tr>
<td>LQT2</td>
<td>234</td>
<td>58 (25)</td>
<td>32 (14)</td>
<td>113 (78)</td>
</tr>
<tr>
<td>LQT3</td>
<td>65</td>
<td>7 (11)</td>
<td>18 (28)</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Total</td>
<td>670</td>
<td>116</td>
<td>84</td>
<td>363</td>
</tr>
</tbody>
</table>

Figure 1. Triggers for cardiac events according to 3 genotypes. Numbers in parentheses indicate number of triggers, not number of patients.
reflects that the present study includes only symptomatic patients.

We also constructed Kaplan-Meyer time-to-event curves specific for the 3 classified triggers within each genotype (Figure 5); they were obviously limited to patients with 1 trigger only. For LQT1 patients through age 8, exercise and emotion occurred at the same time; thereafter, the events triggered by exercise occurred earlier, so by the age of 20, 94% of the patients who were destined to experience events with exercise had them, whereas this was true for only 68% of the patients who were destined to experience episodes during emotional stress. Sleep-related events tended to occur markedly later, and by age 20, 50% of patients still had not experienced a first episode; however, this represents a small subgroup. The patterns for LQT2 and LQT3, despite a similar trend, are less distinct, and the separation between triggers is no longer statistically significant.

Among LQT1 patients, male patients had their first event much earlier than female patients (\(P < 0.0001\)), with the 2 curves beginning to differentiate by age 5 and remaining well distinct over time (Figure 6). Among LQT2 and LQT3 patients, this pattern was just a nonsignificant trend.

**\(\beta\)-Blocker Therapy and Genotype**

Of the 162 LQT1 patients treated with \(\beta\)-blockers and for whom adequate information was available, 131 (81%) had no recurrences (Table 4). Among those (19%) with recurrences, there were 7 cardiac arrests/sudden deaths, representing 4% of the population treated and 23% of those with recurrences.

**Discussion**

This study demonstrates that life-threatening arrhythmias in LQTS patients do not occur at random and that the probability for these events to occur under specific circumstances varies in a gene-specific manner. The unique dimensions of the study, in terms of the number of patients of known genotype who have also experienced a major cardiac event, ensure the validity of the observations and the possibility of extrapolation of these results to all LQTS patients with mutations on these 3 genes.

The results provide new insights into the mechanisms that relate the molecular abnormalities to the onset of lethal arrhythmias and suggest gene-specific approaches to decrease arrhythmic risk.

**Findings and Mechanisms**

The first difference that emerges from an examination of the patterns of association between various triggering conditions

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**Table 3. Genotype and Specific Triggers**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Auditory stimuli</th>
<th></th>
<th>Swimming</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LQT1</td>
<td>LQT2</td>
<td>LQT3</td>
</tr>
<tr>
<td></td>
<td>7/320 (2%)</td>
<td>45/176 (26%)</td>
<td>4/58 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LQT1</td>
<td>LQT2</td>
<td>LQT3</td>
</tr>
<tr>
<td></td>
<td>107/320 (33%)</td>
<td>1/176 (0.6%)</td>
<td>0/58</td>
</tr>
</tbody>
</table>

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**Figure 2.** Lethal cardiac events according to 3 classified triggers in 3 genotypes. Numbers in parentheses indicate number of patients.

**Figure 3.** Mean \(\pm\) 1 SD duration of QT interval, corrected for heart rate (QTc), among 3 genotypes, and according to sex. Numbers in parentheses indicate patients.

**Figure 4.** Kaplan-Meier cumulative survival curves showing time interval between birth and first cardiac event (syncope, resuscitated cardiac arrest, sudden death). Numbers in parentheses indicate patients. It is important to remember that figure and study do not include asymptomatic patients. LQT1 vs LQT2, \(P < 0.0001\). LQT1 vs LQT3, \(P = 0.0001\). LQT3 vs LQT2, \(P = \) NS.
and genotype is that LQT2 patients are more similar to LQT3 patients than to LQT1 patients. Because both LQT1 and LQT2 patients have mutations of \( K_{\text{1}} \) channels, this was initially surprising. The most likely explanation lies in the common denominator for LQT2 and LQT3: the presence of a normal \( I_{\text{Ks}} \) current. \( I_{\text{Ks}} \) is activated by fast heart rates and by catecholamines and shortens ventricular repolarization, thus providing a physiological protection against the possibility of reentrant arrhythmias at fast rates. This may help explain why, compared with LQT1 patients, LQT2 and LQT3 patients are at relatively low risk during exercise. This pattern is further accentuated when the analysis is limited to lethal events, and the similarity between LQT2 and LQT3 becomes quite impressive.

Experimental observations and preliminary clinical data on QT changes during exercise and nighttime provide additional explanations for the low risk during exercise and the high risk during sleep of LQT3 patients. A significant reduction in action potential duration during rapid pacing was observed in the cellular model for LQT3 but not in the model that mimics LQT2. A potential explanation is available. With rapid rates, \( Na^+ \) accumulates in the cell, lowering the \( Na^+ \) gradient across the membrane and, consequently, the magnitude of \( I_{\text{Na}} \). The effect of such a reduction would be negligible during the rising phase of the action potential, when \( I_{\text{Na}} \) is of overwhelming magnitude. However, the plateau \( I_{\text{Na}} \) contribution of the mutant channels is of much smaller magnitude due to delayed inactivation of \( I_{\text{Na}} \) and could be significantly affected by such changes. Of importance, this current operates at a critical time, when the action potential is determined by a delicate balance of small currents. Thus, a reduction in \( I_{\text{Na}} \) during this phase, as can result from faster heart rates, could shorten action potential duration and, hence, the QT interval.

LQT3 patients tend to have shortened QT intervals, much more than normal, during exercise-induced tachycardia and to

**TABLE 4. Genotype and \( \beta \)-Blocker Therapy**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No Recurrences, ( n ) (%)</th>
<th>Recurrences, ( n ) (%)</th>
<th>Cardiac Arrest/Sudden Death, ( n ) (% of all patients/% of patients with recurrences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1 (n=162)</td>
<td>131 (81)</td>
<td>31 (19)</td>
<td>7 (4/23)</td>
</tr>
<tr>
<td>LQT2 (n=91)</td>
<td>54 (59)</td>
<td>37 (41)</td>
<td>4 (4/11)</td>
</tr>
<tr>
<td>LQT3 (n=18)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td>3 (17/33)</td>
</tr>
</tbody>
</table>
have significant QT prolongations at long cycle lengths.\(^7\) They also have considerably prolonged QT intervals during nighttime, whereas this seems to happen to a lesser degree for LQT2 patients and not at all for LQT1 patients.\(^{13}\) Confirmation of these preliminary data would help to explain the current findings, including the intriguing propensity of LQT3 patients to experience major arrhythmic events while they are asleep.

LQT1 patients, with malfunctioning \(I_{\text{Ks}}\) channels, are expected to shorten their QT intervals during tachycardia less effectively than normal individuals. The superimposition of a major catecholamine release, as happens during exercise, without a proper QT adaptation (ie, QT shortening), sets the stage for early afterdepolarizations, which may then lead to TdP via reentry. This concept is supported by an experimental model for LQT1 in which \(I_{\text{Ks}}\) blockade greatly enhances the probability of TdP in the presence of catecholamines.\(^{14}\)

Among these symptomatic LQT1, LQT2, and LQT3 patients, the QT interval was equally prolonged. The apparent discrepancy from our previous report\(^{15}\) is explained by the fact that it included both symptomatic and asymptomatic patients.

We also extended previous observations on the age and sex dependence of first cardiac events.\(^{11}\) The earlier occurrence of cardiac events among male patients reported for nongenotyped LQTS patients is indeed mostly dependent on LQT1. This trend is present across genotypes but is much less distinct among LQT2 and LQT3 patients, where, at variance with LQT1, the difference between sexes is no longer evident after age 20.

**Implications for Clinical Management**

These novel findings allow a more tailored approach to the management of LQTS patients on the basis of genotype.

The greater probability of becoming symptomatic under one condition does not exclude the possibility of a cardiac event occurring under different circumstances. Nevertheless, patients of a given genotype are more or less likely to experience cardiac events under well-defined conditions; this can provide guidance for diagnostic procedures and for gene-specific approaches to management. Indeed, 65% of the patients continue to experience their cardiac events under conditions similar to their first classified event.

The critical role of an impairment of \(I_{\text{Ks}}\) in the facilitation of adrenergic-dependent arrhythmias has implications for therapy. Indeed, 88% of LQT1 patients were at risk during conditions of sympathetic hyperactivity, exercise, or emotions. Thus, antiadrenergic interventions were expected to be particularly effective for them. They did very well with \(\beta\)-blocker therapy; >80% remained free from recurrences, with a total mortality rate of 4%. Only a few LQT1 patients will require therapy other than antiadrenergic intervention.

Most LQT1 patients experience their events during exercise; accordingly, not only should they not engage in competitive sports, like all LQTS patients, but also physical stress should be avoided or limited, compatible with quality of life. Swimming, identified early as an important trigger for LQTS patients\(^{16}\) and recently for LQT1 patients,\(^8\) is a major risk factor (triggering an event in 33% of them), and without supervision, swimming should be avoided. Because LQT1 patients are endangered by high heart rates, pacemaker therapy is not advised.

LQT3 patients are at higher risk at longer cycle lengths. This raises concerns, not yet supported by evidence, regarding the use of \(\beta\)-blockers because of the attendant reduction in heart rate. The prevention of norepinephrine release remains important, but it is effectively and more safely achieved with selective left cardiac sympathetic denervation,\(^{17}\) which does not reduce heart rate.\(^{18}\) LQT3 patients may benefit from pacemakers, which would also allow the safe use of \(\beta\)-blockers, because their QT interval tends to shorten significantly at faster heart rates; accordingly, recreational physical activity may not have to be withheld, except for those who have already experienced events during exercise. The long-term value of \(\text{Na}^+\) channel blockers in this group, proposed in 1995,\(^7\) remains to be tested. Even though the data regarding therapy for LQT3 patients remain numerically limited, their high mortality rate despite therapy, and particularly at the first episode,\(^{4}\) suggests the consideration of internal cardioverter-defibrillator implantation; the combination with left sympathectomy would reduce the probability of lethal arrhythmias while providing a safety net.

Gene-specific management for LQT2 is more problematic. Suggestions that increases in extracellular \(\text{K}^+\) concentration may be beneficial are hindered by the difficulties in achieving high [\(\text{K}^+\)] with chronic oral therapy. These patients are at a relatively low risk during exercise. The occurrence of cardiac events either at sleep/rest without arousal or during exercise, given the extremely low probability of their occurrence under both conditions, can identify the triggers associated with the highest risk. A comparison with LQT1 patients suggested that auditory stimuli are specific for LQT2\(^{19}\); our data, which demonstrate their occurrence mostly during sleep, support but also qualify that concept by confirming the high prevalence of auditory stimuli as triggers for LQT2 and by showing their significant role also for LQT3 patients. The experimental prevention with \(\beta\)-blocker therapy of life-threatening arrhythmias triggered by a loud noise suggests their effectiveness also for LQT2 patients at risk under this specific condition. The efficacy of \(\beta\)-blockers in LQT2 patients was already proposed.\(^{10}\) Finally, the high risk associated with auditory stimuli makes the removal of telephones and alarm clocks from patient bedrooms advisable.

The cumulative survival curves demonstrate that the age at which LQTS becomes clinically manifest is also gene specific, with LQT1 patients being the youngest to experience cardiac events; 86% of them experience their first episode by age 20. In contrast, symptomatic LQT2 and LQT3 patients are also at risk of the onset of cardiac events later in life. Although data for only symptomatic patients are presented here, when dealing with asymptomatic patients of known genotype, it may now be possible to consider their probability of ever becoming symptomatic on the basis of their age. This allows further refinement in management strategy.

**Study Limitations**

This study has the limitations that are unavoidable with multiple data sources, such as occurs in any registry or large
multicenter studies. Due to organizational complexity, data collection forms were very simple, with only information essential for the present study on triggers. Data on secondary objectives, such as response to therapy, should be regarded as hypothesis generating, and will require specific analysis with additional information. Nevertheless, the very large number of genotyped symptomatic patients allows to safe conclusions to be drawn regarding the main aspects of the study.

Conclusions
This uniquely large cooperative study has allowed us to gather information on an unprecedented number of LQTS patients, all with major cardiac events and all of known genotype. In the investigation of hereditary arrhythmogenic disorders, this is the largest data set ever used for genotype-phenotype correlation studies. It provides definitive evidence for genotype-specific differences in the propensity to life-threatening arrhythmias under specific conditions and offers insights into some of the underlying mechanisms. It also provides the rationale for a novel approach toward the prevention of sudden death in LQTS on the basis of the integration of experience-supported therapies (β-blockers, left cardiac sympathetic denervation, pacemakers, implantable cardioverter-defibrillators) with behavioral recommendations and therapeutic choices dictated by gene-specific considerations.

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