Risk of Syncope in Family Members Who Are Genotype-Negative for a Family-Associated Long-QT Syndrome Mutation

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Background—Current clinical diagnosis of long-QT syndrome (LQTS) includes genetic testing of family members of mutation-positive patients. The present study was designed to assess the clinical course of individuals who are found negative for the LQTS-causing mutation in their families.

Methods and Results—Multivariate Cox proportional hazards model was used to assess the risk for cardiac events (comprising syncope, aborted cardiac arrest [ACA], or sudden cardiac death [SCD]) from birth through age 40 years among 1828 subjects from the LQTS Registry who were found negative for their family LQTS-causing mutation. The median QTc of study subjects was 423 ms (interquartile range, 402–442 ms). The cumulative probability of a first syncope through age 40 years was 15%. However, only 2 patients (0.1%) had ACA, and none died suddenly during follow-up. Independent risk factors for syncope in genotype-negative subjects included female sex (hazard ratio [HR], 1.60; P=0.002), prolonged QTc (HR=1.63 per 100 ms increment, P=0.02), family history of ACA or SCD (HR=1.89, P=0.002), and LQT2 versus LQT1 family mutation (HR=1.41, P=0.03). Subgroup analysis showed that the presence of the K897T polymorphism in the LQT2 gene in an affected family was associated with an 11-fold (P=0.001) increase in the risk of recurrent syncope in genotype-negative subjects.

Conclusions—Our findings suggest that cardiac events among genotype-negative family members of LQTS patients are dominated by nonfatal syncopal episodes without occurrence of sudden cardiac death. The risk for nonfatal events in this population may be mediated by the presence of common polymorphisms in LQTS genes. (Circ Cardiovasc Genet. 2011;4:491-499.)

Key Words: gene mutation ■ genetic polymorphisms ■ long-QT syndrome ■ SCD ■ syncope

Congenital long-QT syndrome (LQTS) is an inherited channelopathy associated with variable penetrance, prolongation of the heart-rate corrected QT interval (QTc), and an increased risk for syncope and sudden cardiac death (SCD) due to ventricular tachyarrhythmias. Genetic testing provides important information for diagnosis, risk stratification, and treatment of patients with LQTS. To date, more than 600 mutations have been identified in 13 LQTS genes, with the LQT1, LQT2, and LQT3 genotypes comprising more than 95% of genotype-positive LQTS and approximately 75% of all patients with LQTS.

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The current clinical diagnosis of congenital LQTS includes genetic testing of family members of identified LQTS probands. However, the clinical course of individuals who are found negative for the LQTS-causing family mutation is unknown. Specifically, data regarding the risk for syncope and life-threatening events in this population are limited. Accordingly, the present study was carried out in a large cohort of genotype-negative family members from genotype-
positive families enrolled in the International LQTS Registry. We investigated the risk for, and the factors associated with, cardiac events in this mutation-negative group of patients.

Methods

Study Population

Patients were included in the study if they were genetically tested and found negative for the family’s LQT3 causing mutation (KCNQ1, KCNH2, or SCN5A). Subjects related to family probands who had multiple gene mutations were excluded from the study. The current study included patients from the United States and Israeli portions of the international LQTS Registry since only patients from these centers met the inclusion criteria of genetic testing among family members of LQTS mutation positive patients. The final study sample comprised 1828 subjects who were genotype-negative for a known family mutation. All subjects or their guardians provided informed consent for the genetic and clinical studies.

Genotype Characterization

The KCNQ1, KCNH2, and SCN5A mutations were identified with the use of standard genetic tests performed in academic molecular-genetic laboratories (including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; Mayo Clinic College of Medicine, Rochester, MN; and Boston Children’s Hospital, Boston, MA) and by commercial genetic laboratories (including GenEdx, Gaithersburg, MD; and PGx Health [FAMILION], New Haven, CT).

Data regarding the existence of LQTS-related gene polymorphisms, in addition to the LQTS-causing mutation, were collected for first-degree family members of 218 study subjects. LQTS-gene polymorphisms were evaluated in the 5 most common LQTS genes: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. The frequency of the specific polymorphism in the families of the 218 study subjects, by family LQTS mutation, is presented in the online-only Data Supplement Appendix (online-only Data Supplement Table I).

Phenotype Characterization

Routine clinical and ECG parameters were acquired at the time of enrollment. Follow-up was censored at age 41 years to minimize the influence of coronary and acquired heart disease on cardiac events. Measured parameters on the first recorded ECG included QT and R-R intervals in milliseconds, with QT corrected for heart rate by the Bazett formula. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiographic findings, therapy, and the occurrence of cardiac events. Information on end-point events was determined from the clinical history ascertained by routine follow-up contact with the patient, family members, attending physician, or the medical records. No implantable cardioverter-defibrillator (ICD) events were recorded in this population.

End Points

The primary end point of the present study was prespecified as the occurrence of a first cardiac event, comprising syncope (defined as transient loss of consciousness being abrupt in onset and offset), aborted cardiac arrest ([ACA] requiring external defibrillation as part of the resuscitation), or LQTS-related sudden cardiac death ([SCD] abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting). Since only 2 study subjects had ACA and none had SCD during follow-up, syncope is reported as the primary end point, and the risk for recurrent syncope was assessed as a secondary end point. The circumstances of the syncopal events (including data on onset, prodromal symptoms, and seizures) were corroborated by the study coordinators through the patient’s medical files and interviews with individuals about themselves or about family members, and categorized by the study specialists using prespecified codes.

Statistical Analysis

Characteristics of the 3 subgroups of patients categorized by family proband’s LQTS-causing mutation (LQT1, LQT2, and LQT3) were compared with the χ² test and the Fisher exact test for categorical variables and ANOVA test or the Kruskal-Wallis 1-way ANOVA for continuous variables.

The overall incidence rate of syncope and the incidence rates for syncope with specific age and sex subgroups were calculated by dividing the number of subjects with syncope by the total number of person-years of follow-up in each subgroup. The probability of a first syncope was graphically displayed by QTc, sex, and family mutation according to the method of Kaplan and Meier, with comparison of cumulative probability of events by the log-rank test. A Mantel-Byar graph was used for displaying cumulative risk for the time-dependent covariate of the occurrence of a life-threatening cardiac event in a first-degree family member. This analysis accrues patients over time, in whom a life-threatening cardiac event occurs in a first-degree family member during follow-up, and accounts for time-varying entry into this group.

The Cox proportional-hazards survivorship model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of syncope from birth through age 40 years. Prespecified covariates in the multivariate model included sex, baseline QTc (dichotomized at the upper quartile value [≥440 ms] and assessed also as continuous measure [per 100 ms increment]), the family gene mutation, a family history of life-threatening cardiac event in a first-degree relative, and treatment with β-blockers. Family history of life-threatening cardiac event and the administration of β-blocker therapy from birth to age 40 years in a study individual were evaluated as time-dependent covariates. In a secondary analysis, among the 218 genotype-negative patients on whom polymorphism data were available, we used the conditional model proposed by Prentice, Williams, and Peterson (PWP), to evaluate the risk for recurrent syncope events. This model assumes a subject cannot be at risk for event 2 until event 1 occurs. It simultaneously models the distribution of the time to first syncope and the gap times between subsequent syncopal events as functions of risk factors of interest. Prespecified covariates that were included as potential predictors of recurrent syncope were sex, QTc at baseline, family history of life-threatening cardiac event in a first-degree relative, treatment with β-blockers, the presence of a polymorphism and the specific type of polymorphism in a first-degree affected family member. All models were stratified by the decade in which study patients were born to account for changes in the baseline hazard function for different calendar time periods. The effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership. All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, NC). A 2-sided 0.05 significance level was used for hypothesis testing.

Results

Study Population

Of the total 1828 subjects (239 families) who were genetically tested and found negative for the family’s LQTS-causing mutation, there were 696 subjects from 109 families with LQT1 mutations, 816 subjects from 108 families with LQT2 mutations, and 316 subjects from 22 families with LQT3 mutations. The median (interquartile range) number of members of a family was 4 (2–9) (including genotype-positive and genotype-negative patients). The current study
population comprised up to 4th-degree genotype-negative relatives of probands (22% of subjects were first-degree relatives of the proband, 25% second-degree, 32% third-degree, and 20% fourth-degree).

The clinical characteristics of all study subjects and of the subgroups categorized by their family’s LQTS-causing mutation are presented in Table 1. The median QTc (interquartile range) of the study cohort was 423 ms (402–442 ms); there were no significant differences among the 3 subgroups with regard to sex, QTc at baseline, or the proportion of subjects with a family history of life-threatening cardiac events. However, during follow-up medical treatment with β-blockers and the frequency of cardiac events were highest among study subjects with a family LQT2 mutation (Table 1).

The baseline clinical and ECG characteristic of study subjects with and without collected data regarding the coexistence of family polymorphisms were similar (not shown). Among the 218 study subjects for whom data regarding the coexistence of family polymorphisms were collected, the highest frequency of family polymorphisms (and specifically the K897T polymorphism in the KCNH2 gene) was observed among subjects from LQT2 families (Table 1).

### Risk of Syncope in Genotype-Negative Family Members

Almost all cardiac events were nonfatal syncope; only 2 study subjects (0.1%) had ACA or SCD during follow-up. The cumulative probability of a first syncope at age 40 years among the 1828 genotype-negative study subjects was 15%. The overall incidence rate of a first syncope event was 4.2 per 1000 person-years. The incidence rate increased after the age of 10 and was higher in women than in men (Figure 1). One hundred one subjects (5.5%) had 1 or more recurrences of syncope. The overall incidence rate of recurrent syncope events was 8.6 per 1000 person-years.

Consistent with the incidence rates, the cumulative probability of a first syncope by age 40 years was higher among women as compared with men (18% versus 11%, respectively; \( P = 0.002 \)) for a first syncope as compared with patients without a family history for life-threatening cardiac events (Table 2).

Among subjects with a family history of life-threatening cardiac event had a 1.4-fold increased risk for a first syncope as compared with those with an LQT1 or LQT3 family mutation (20%) as compared with those with an LQT2 family mutation (20%) (Figure 2A). In addition, the rate of syncope events was higher among subjects with an LQT2 family mutation (20%) as compared with those with an LQT1 or LQT3 family mutation (12% and 10%, respectively; \( P = 0.03 \)) for a first syncope as compared with lower QTc values (19% versus 14%, respectively; \( P = 0.01 \)) for a first syncope as compared with lower QTc values (19% versus 14%, respectively; \( P = 0.01 \)). Mantel-Byar survival analysis showed that the occurrence of a life-threatening event in a genotype-positive sibling was associated with a significant increase in the risk of a subsequent syncope in genotype-negative family members (Figure 3).

Multivariate analysis in the total study population (Table 2) showed consistent results regarding the high-risk factors that were identified in the univariate analyses. Thus, women had a significant 1.6-fold increased risk as compared with men (\( P = 0.002 \)); subjects with family-associated LQT2 mutations had a 1.4-fold increased risk for a first syncope as compared with family-associated LQT1 mutations (\( P = 0.03 \)); and those with a family history of life-threatening cardiac event had nearly a 2-fold increased risk (\( P = 0.002 \)) for a first syncope as compared with patients without a family history for life-threatening cardiac events (Table 2).

Subgroup analysis, among the 218 study subjects for whom data regarding the coexistence of LQTS-gene polymorphisms in affected first-degree family members were
collected, showed that the cumulative probability of a first syncope at age 40 years was significantly higher among genotype-negative subjects with a family LQTS-gene polymorphism (25%) as compared with those in whom a family polymorphism was not present (5%; P=0.004; Figure 4). Consistently, a secondary analysis that assessed the risk for recurrent syncope in the same subgroup (Table 3), showed that the presence of an LQTS-gene polymorphisms in an affected first-degree relative was associated with an 8-fold (P<0.001) increase in the adjusted risk for recurrent syncope in a genotype-negative study subject. Specifically, the coexistence of the K897T polymorphism in the LQT2 gene in affected family members was associated with the highest risk (hazard ratio [HR]=11.1; P<0.001) for recurrent syncope in genotype-negative study subjects (Table 3).

Medical therapy with β-blockers was not associated with a statistically significant reduction in the risk of a first syncope in the total study population (HR=0.42; P=0.23 [Table 2]), but was associated with a significant 71% (P=0.02) risk reduction in the risk of recurrent syncope in genotype-negative subjects.

Figure 1. Incidence rate of syncope by age and sex. The incidence rate of first syncope event per 1000 person-years was calculated by dividing the number of subjects with syncope by the total number of person-years of follow-up in each sex-age subgroup.

Figure 2. Probability of syncope by clinical risk factors. Kaplan-Meier estimates of the probability of syncope from birth to 40 years of age by (A) sex; (B) family long-QT syndrome genotype; and (C) QTc duration.
reduction in the model that evaluated the risk of recurrent syncope (Table 3), suggesting that this therapeutic modality may be effective in symptomatic family members of LQTS patients.

There was no statistical significant difference in the effect of β-blockers among the different family genotypes, or in the effect of β-blockers among women during pregnancy and post partum period. Additional secondary analyses stratifying country of origin (US and Israeli centers) showed similar results for all analyses.

Risk for Life-Threatening Cardiac Events
Only 2 subjects, comprising 0.1% of this study cohort, had aborted cardiac arrest during follow-up and none died due to SCD during follow-up. The characteristics of the 2 patients are shown in Table 4. Both patients were female who had an LQT2-causing family mutation and the K897T polymorphism in the LQT2 gene. One patient had an ACA at the age of 14 years during a volleyball game, which was her first cardiac event. The other patient had syncope at the age of 6 years during vigorous physical activity while traveling down a snowy hill with a sled and had an aborted cardiac arrest at the age of 24 during delivery of her first child. Both patients were not treated with β-blockers at the time of the event (Table 4).

Discussion
In the present study, we assessed the clinical course and risk factors for cardiac events among subjects who were genetically tested and found negative for the family proband’s LQTS-causing mutation. Our findings suggest that (1) genotype-negative family members of LQTS patients have a 15% rate of nonfatal syncope events, but a near zero (0.1%) of life-threatening events; and (2) specific clinical and genetic factors identify increased risk for syncope in this population. These findings can be used to guide risk assessment and management of family members of LQTS patients.

The availability of genetic testing and advancements in the understanding of the genetics of LQTS have demonstrated the importance of this information in the diagnosis of LQTS,16–17 understanding the clinical differences between individual genetic disorders, and improved risk stratification and management strategies.4,6,18 Screening for the patient’s genotype, usually for the common genes (ie, KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2), can be completed in several weeks. If a mutation is found, the cost of genotype testing can be reduced substantially by checking only for the mutation found in the proband.19 Thus, carrying out genetic testing for the mutation identified in a family member has become a common practice for the diagnosis of LQTS. Patients identified as positive for the family-causing mutation are managed on the basis of their molecular diagnosis and clinical symptoms. In contrast, currently there are no data regarding the clinical course of asymptomatic and symptomatic genotype-negative family members of LQTS patients.

In the present study, we evaluated the risk for syncope and life-threatening cardiac events in 1828 subjects from the International LQTS Registry who were genetically tested and found negative for the family proband’s LQTS-causing mutation. Genotype-negative family members of LQTS patients were shown to have a 15% cumulative rate of cardiac events up to the age of 40 years. However,

| Table 2. Multivariate Analysis: Predictors of First Syncope in the Total Study Population |
|-----------------|-----------------|-----------------|-----------------|
| Hazard Ratio    | 95% Confidence Interval | P Value |
| Female          | 1.60            | 1.19–2.15       | 0.002           |
| QTc at baseline, every 100 ms* | 1.63            | 1.09–2.46       | 0.02            |
| QTc at baseline ≥440 ms* | 1.49            | 1.11–2.01       | 0.009           |
| Time-dependent family history of aborted cardiac arrest/ sudden cardiac death | 1.89            | 1.26–2.83       | 0.002           |
| Family LQT2 vs family LQT1 | 1.41            | 1.03–1.91       | 0.03            |
| Family LQT2 vs family LQT3 | 1.77            | 1.14–2.76       | 0.01            |
| Time-dependent β-blocker treatment | 0.42            | 0.10–1.72       | 0.23            |

*The effects of QTc at baseline (continuous measure) and QTc >440 ms on outcome were evaluated in separate models; findings for other covariates are reported from the model in which QTc was assessed as a continuous measure.
virtually all cardiac events in this patient subset comprised nonfatal syncopal events. Furthermore, none of the patients had SCD during follow-up. Thus, children and young adults who undergo genetic testing and are identified as negative for a mutation in a family member can be reassured of a favorable long-term outcome even if nonfatal symptoms occur during follow-up.

Independent risk factors associated with increased risk for nonfatal cardiac events in study patients included female sex, prolonged QTc, family history of life-threatening cardiac events, and LQT2 family mutation. The latter association between LQT2 family mutation and increased risk for syncope events may be related to a higher prevalence of LQTS gene polymorphism among individuals with a LQT2 family mutation, and particularly a greater prevalence of the common single nucleotide polymorphism $K897T$ present in the $KCNH2$ gene. Indeed, several studies demonstrated that LQTS gene polymorphisms lead to $KCNQ1$ or $KCNH2$ channel loss of function,20,21 increased risk for cardiac events in congenital LQTS patients20–23 and increased risk for developing drug-associated torsade de pointes.24 It was also suggested that $K897T$ polymorphism may increase the risk for torsade de pointes and ventricular fibrillation following acute myocardial infarction.25,26 However, it should be noted that the role of $K897T$ polymorphism in LQTS is controversial with several large-scale population studies showing that $K897T$ polymorphism is associated with either shortening or prolongation of the QTc interval.27–30

Herein we found in a subgroup of genotype-negative subjects, for whom data regarding the presence of LQTS gene polymorphism in a first-degree relative were available, that LQTS gene polymorphisms in general, and the $K897T$ polymorphism specifically, were the most powerful

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Table 3. Multivariate Analysis: Predictors of Recurrent Syncope Events Among 218 Patients With Data on Family Polymorphism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any polymorphism</td>
<td>8.31</td>
<td>2.69–25.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple polymorphisms vs no polymorphism</td>
<td>8.85</td>
<td>2.79–28.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single polymorphism vs no polymorphism</td>
<td>7.73</td>
<td>2.18–27.46</td>
<td>0.002</td>
</tr>
<tr>
<td>$K897T$ vs no polymorphism</td>
<td>11.10</td>
<td>2.79–44.12</td>
<td>0.001</td>
</tr>
<tr>
<td>$G38S$ vs no polymorphism</td>
<td>7.98</td>
<td>1.97–32.32</td>
<td>0.004</td>
</tr>
<tr>
<td>$H858R$ vs no polymorphism</td>
<td>1.69</td>
<td>0.22–13.08</td>
<td>0.616</td>
</tr>
<tr>
<td>Time dependent $\beta$-blocker treatment</td>
<td>0.29</td>
<td>0.10–0.86</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adjusted also for sex, QTc at baseline, and time-dependent family history of aborted cardiac arrest or sudden cardiac death.

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Table 4. Clinical Characteristics of Patients With Aborted Cardiac Arrest

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Event at time of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc at enrollment, ms</td>
<td>400</td>
<td>454</td>
<td></td>
</tr>
<tr>
<td>No. of cardiac events</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age of first cardiac event, y</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Trigger for first cardiac event</td>
<td>Playing volleyball</td>
<td>Vigorous physical activity</td>
<td></td>
</tr>
<tr>
<td>Age of aborted cardiac arrest, y</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Trigger for aborted cardiac arrest</td>
<td>Playing volleyball</td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Family mutation</td>
<td>G601S (in $KCNH2$)</td>
<td>W568fsX593 (in $KCNH2$)</td>
<td></td>
</tr>
<tr>
<td>Genes tested in patient</td>
<td>$KCN01$, $KCNH2$, $SCN5A$, $KCNE1$, $KCNE2$</td>
<td>$KCN01$, $KCNH2$, $SCN5A$, $KCNE1$, $KCNE2$</td>
<td></td>
</tr>
<tr>
<td>Polymorphism in patient</td>
<td>Data unavailable</td>
<td>$K897T$ (in $KCNH2$)</td>
<td></td>
</tr>
<tr>
<td>Polymorphism in 1&lt;sup&gt;st&lt;/sup&gt;-degree relative</td>
<td>$K897T$ (in $KCNH2$)</td>
<td>$K897T$ (in $KCNH2$)</td>
<td></td>
</tr>
<tr>
<td>Deafness</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Life threatening cardiac event in 1&lt;sup&gt;st&lt;/sup&gt;-degree relative</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>Mitral valve prolapse</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Treatment with $\beta$-blockers</td>
<td>After aborted cardiac arrest</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>After aborted cardiac arrest</td>
<td>Never</td>
<td></td>
</tr>
</tbody>
</table>
predictors of recurrent syncope in this population. Thus, genotype-negative subjects with a family polymorphism in an LQTS gene had an 8-fold increase in the risk of recurrent syncope, and genotype-negative subjects with the K897T polymorphism had a pronounced 11-fold increase in the risk of this end point. In addition, K897T polymorphism in affected first-degree family members was associated with increased risk for syncope without evidence of a significant QTc prolongation or with a mildly prolonged QTc. These findings suggest the possibility that mild abnormalities in ion channel current associated with a single nucleotide polymorphism may increase the risk of nonfatal self-limited ventricular tachyarrhythmias in genotype-negative family members of LQTS patients with a normal-range or a mildly prolonged QTc.

Chronic treatment with estradiol was shown to be associated with QT prolongation secondary to drug therapy.31,32 Consistent with this mechanism, female sex was associated with a significant increase in the risk for syncope in the study population. Furthermore, the 2 genotype-negative patients who had ACA during follow-up were women, who had the event after the onset of adolescence period in women from families with the K897T polymorphism during higher risk conditions such as exercise or the postpartum period. Thus, a combination of environmental, physiological, and genetic factors may predispose to the occurrence of arrhythmic events in genotype-negative family members of LQTS patients.

Most recently, it was shown that the risk for a first cardiac event of any type (comprising mainly nonlife-threatening syncopal episodes) and the risk of a first life-threatening cardiac event (comprising ACA/SCD) were highest among genotype-positive patients with QTc >440 ms, intermediate among genotype-positive patients with QTc 440 ms and lowest among genotype-negative patients.33 Data on the incidence rate of syncope in the general population are limited and conflicting. Thus, it is difficult to compare the incidence of first syncope in the present study population with the incidence in the general population. The Framingham Heart Study, evaluating 7814 participants (age range, 20–96 years) over an average follow-up of 17 years, reported an incidence rate of 3 to 4 events (first syncope) per 1000 person-years during the third and fourth decades of life.34 The present study showed a higher incidence rate, with 6.1 and 4.3 events per 1000 person-years during the third and fourth decades of life respectively (with the incidence rate more than doubled among women), suggesting increased frequency of nonfatal syncopal episodes in family members of LQTS patients. The reported ACA/SCD event rate among children and adolescents from the general population ranges from 2 to 20 per 100 000 person-years35–40; the present study showed an ACA/SCD event rate of 4 per 100 000 person years.

**Limitations**

Because study subjects were tested only for the mutation that was identified in an affected family member, we cannot rule out that patients who had syncope had other LQTS-causing mutations or other genetic syndromes associated with ventricular tachyarrhythmias.

Genetic testing for the presence of LQTS-gene polymorphisms was carried out among family members of only 218 study subjects. However, despite the smaller sample size, the results in this subgroup showed an independent and a powerful association between the presence of LQTS-gene polymorphisms in general (and the K897T polymorphism in the KCNH2 gene, specifically) and the risk for recurrent syncope events, suggesting that this genetic factor may contribute to increased risk for nonfatal events in genotype-negative subjects. It should also be noted that only affected first-degree relatives were tested for LQTS-gene polymorphisms. However, it is conceivable that genotype-negative subjects also had increased frequency of polymorphisms that were identified in their first-degree family members.

We did not identify a statistical significant difference in the effect of β-blockers among the different family genotypes, or in the effect of β-blockers among women during pregnancy and post partum period. We did not identify a polymorphism that has a protective effect in LQTS. However, the current study may be underpowered to detect these effects.

**Summary, Implications, and Future Research**

Human genetic variation is facilitating an understanding of why susceptibility to diseases varies among individuals. The present study among 1828 subjects from the large LQTS Registry suggests that the presence of a latent genetic background may affect the risk for nonfatal cardiac events even among subjects who were genetically tested and found negative for the family proband’s LQTS-causing mutation. These subjects were shown to have similar rate of life-threatening cardiac events as the general population. Thus, based on these findings subjects who are tested negative for their family members LQTS-causing mutation could be reassured of a benign course regardless of the occurrence of symptoms or the presence of risk factors. Our findings also suggest that β-blocker therapy can be used to reduce the risk of syncope among symptomatic genotype-negative subjects, especially those with high risk factors (including women, subjects with mildly prolonged QTc, those with family history of life-threatening cardiac events, and those with family members with a KCNH2 gene mutation or polymorphism).

Further research is needed to determine the effect of LQTS-gene polymorphisms on the clinical course of patients with congenital LQTS and their family members and how these effects relate to the risk for nonfatal arrhythmic events in the general population or in those who have drug-induced LQTS.

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References

**CLINICAL PERSPECTIVE**

The current clinical diagnosis of congenital long-QT syndrome (LQTS) includes genetic testing of family members of identified LQTS probands. However, the clinical course of individuals who are found negative for the LQTS-causing family mutation is unknown. We assessed the clinical course and risk factors for cardiac events among subjects who were genetically tested and found negative for the family proband’s LQTS-causing mutation enrolled in the International LQTS Registry. The present study, among 1828 subjects from the large LQTS Registry, suggests that specific clinical and genetic factors identify increased risk for syncope in this population, including female sex, prolonged QTc, family history of life-threatening cardiac events, LQT2 family mutation, and the presence of specific single nucleotide polymorphisms (eg, K897T polymorphism in the LQT2 gene). The cumulative probability of a first cardiac event through age 40 years was 15%. However, only 2 patients (0.1%) had fatal or near fatal events during follow-up. Thus, our findings suggest that subjects who are tested negative for their family members’ LQTS-causing mutation probably have an overall benign course.
Risk of Syncope in Family Members Who Are Genotype-Negative for a Family-Associated Long-QT Syndrome Mutation

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Supplemental Material

Table 1S. Distribution of LQTS gene polymorphism among affected first degree relatives of study subjects.

<table>
<thead>
<tr>
<th>Polymorphism in 1st degree relative</th>
<th>All subjects (n=218)</th>
<th>Family mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LQT1 (n=44)</td>
<td>LQT2 (n=127)</td>
</tr>
<tr>
<td>K897T (KCNH2)</td>
<td>82</td>
<td>14</td>
</tr>
<tr>
<td>H558R (SCN5A)</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>A572D (SCN5A)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>F2004L (SCN5A)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>G38S (KCNE1)</td>
<td>121</td>
<td>21</td>
</tr>
<tr>
<td>D85N (KCNE1)</td>
<td>29</td>
<td>2</td>
</tr>
</tbody>
</table>

Data on LQTS gene polymorphism among affected first degree relatives of study subjects were available for 218 subjects. A hundred and one subjects had more than one type of family LQTS gene polymorphism. LQTS gene polymorphism was evaluated for the 5 most common LQTS genes: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2.