Follow-Up of 316 Molecularly Defined Pediatric Long-QT Syndrome Patients
Clinical Course, Treatments, and Side Effects

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Background—Inherited long-QT syndrome (LQTS) is associated with risk of sudden death. We assessed the clinical course and the fulfillment of current treatment strategies in molecularly defined pediatric LQTS type 1 and (LQT1) and type 2 (LQT2) patients.

Methods and Results—Follow-up data covering a mean of 12 years were collected for 316 genotyped LQT1 and LQT2 patients aged 0 to 18 years. No arrhythmic deaths occurred during the follow-up. Finnish KCNQ1 and KCNH2 founder mutations were associated with fewer cardiac events than other KCNQ1 and KCNH2 mutations (hazard ratio [HR], 0.33; P=0.03 and HR, 0.16; P=0.01, respectively). QTc interval ≥500 ms increased the risk of cardiac events compared with QTc <470 ms (HR, 3.32; P=0.001). Treatment with β-blocker medication was associated with reduced risk of first cardiac event (HR, 0.23; P=0.001). Noncompliant LQT2 patients were more often symptomatic than compliant LQT2 patients (18% and 0%, respectively; P=0.03). Treatment with implantable cardioverter defibrillator was rare (3%) and resulted in reinterventions in 44% of cases.

Conclusions—Severe cardiac events are uncommon in molecularly defined and appropriately treated pediatric LQTS mutation carriers. β-Blocker medication reduces the risk of cardiac events and is generally well tolerated in this age group of LQTS patients. (Circ Arrhythm Electrophysiol. 2015;8:815-823. DOI: 10.1161/CIRCEP.114.002654.)

Key Words: arrhythmias, cardiac β-blockers, adrenergic defibrillators, implantable long QT syndrome pediatrics

Long-QT syndrome (LQTS) is an inherited cardiac arrhythmia disorder manifesting with ventricular arrhythmias, syncopal spells, and sudden cardiac death (SCD). LQT1 and LQT2, caused by mutations in the KCNQ1 and KCNH2 genes, respectively, are the most common subtypes of LQTS (40% to 55% and 35% to 45% of the cases, respectively). Studies based on international cohorts show that if left untreated the prognosis of LQTS is poor.1,2 β-blockers are the standard therapy for LQTS and are associated with a significant reduction in cardiac events.4,5 Preventive measures, such as avoidance of QT-prolonging drugs, electrolyte disturbances, and adrenergic stimuli, are essential and apply to all LQTS patients.10

The number of detected asymptomatic mutation carriers is increasing because of cascade genetic screening of LQTS family members. Because of incomplete penetrance,2 LQTS mutation carriers unveiled by cascade screening often show milder phenotype than clinically diagnosed LQTS patients. The recent expert consensus statement on the management of LQTS acknowledges the ambiguity to treat the asymptomatic mutation carriers with β-blockers.10 At the moment, β-blocker medication is recommended even in infancy or early childhood for primary prevention of cardiac events.

Previous follow-up studies on pediatric LQTS patients have mainly consisted of ungenotyped patients.7,8 In the present follow-up study, we assess the clinical course, efficacy, and adverse effects of β-blocker and device therapies in molecularly defined pediatric LQT1 and LQT2 patients. The high prevalence of the 4 founder LQTS mutations in the Finnish population2,11 provided us with an opportunity to assess their mutation-specific prognosis.

Methods

Study Population

The study population was drawn from the Finnish Inherited Cardiac Disorder Registry established in 1991 and comprising 4000...
molecularly tested subjects. Baseline characteristics, including personal and family history of cardiac events, QTc interval using Bazett’s formula, and treatment history were collected at the study enrollment.

The inclusion criteria for this study were (1) genetically confirmed KCNQ1 or KCNH2 mutation, or genetically confirmed non-carrier status of the family-specific LQTS mutation and (2) age <16 years on enrollment. In 2011 to 2012, a questionnaire was sent to the study subjects or their parents. Collected data included occurrence of cardiac events (LQTS-related syncope or aborted cardiac arrest [ACA]), medical therapy, device therapy with a pacemaker or an implantable cardioverter defibrillator (ICD), and left cardiac sympathetic denervation (LCSD). Data regarding β-blocker medication included starting date, discontinuation date if appropriate, type of β-blocker, adverse effects, and compliance defined as forgetting or not taking medication once a month or more often.

Data of all deaths during the follow-up were obtained from Statistics Finland. Clinical data were obtained from hospitals for all patients who had device therapy underwent LCSD, had an ACA, or died. Collected ICD data included implantation indications, complications, revisions, and ICD discharges. Autopsy documents of patients who died during the follow-up were evaluated.

The primary end point of the study was cardiac event comprising LQTS-related syncope, ACA, or SCD which ever occurred first. The follow-up started from birth and ended when subject (1) reached the 2011 to 2012 inquiry, (2) turned 18 years, or (3) deceased. The final study population (n=523) consisted of 258 mutation carriers, and 207 noncarrier relatives. There was no difference between subjects fulfilling the inclusion criteria (n=857) and subjects of the final study cohort (n=523) in respect of proportion of sex, LQTS subtypes, FF mutation, QTc duration categorized as ≥500, 470 to 499, or <470 ms, and time-dependent β-blocker medication as prespecified covariates, was used to evaluate the independent contribution of risk factors to first cardiac event in mutation carriers. The stratified lifetime rate (SRT) was stratified by age and adjusted for family membership using robust sandwich estimators. Non-violation of the proportional hazards assumption was detected as tested by log–log graphs. In an interaction term analysis, no statistically significant interactions were discovered, and thus no interaction terms were included in the multivariate model. A separate QTc missing covariate was used for patients whose baseline QTc data were not available (n=28).

Efficacy of β-blocker medication in preventing cardiac arrhythmia was also evaluated by assessing incidence rates of cardiac events per person-years after initiating β-blocker. In this incidence rate analysis, if a patient already had a cardiac event before beginning of β-blocker, a secondary end point of first cardiac event after initiation of β-blocker was taken into consideration. Statistical analyses were performed using SPSS version 20. A 2-sided P value ≤0.05 was interpreted as statistically significant.

Results

A total of 857 subjects fulfilled the inclusion criteria. Three of them died during the follow-up and 520 (61%) responded to the inquiry. The final study population (n=523) consisted of 316 LQTS mutation carriers (224 KCNQ1 mutation carriers, 85 KCNH2 mutation carriers, and 7 carriers with >1 KCNQ1 or KCNH2 mutation) and 207 noncarrier relatives. There was no difference between subjects fulfilling the inclusion criteria (n=857) and subjects of the final study cohort (n=523) in respect of proportion of sex, LQTS subtypes, FF mutation carriers, and symptomatic patients at the time of diagnosis, or QTc intervals. The final study population comprised 130 families. One family had 4, 1 family had 3, and the rest of the families had 0 to 2 cardiac events during the follow-up. Of the 316 mutation carriers, 40 (13%) were probands. Altogether 28 (9%) were symptomatic at diagnosis. Mean age at enrollment (±age at diagnosis) was 5.8±5.4 years, prospective follow-up described.12,14 Mutations were categorized by mutation type as missense or nonmissense (nonsense, frameshift, splice site, insertion, or deletion) mutations and by their location as previously described.12,14 Patients carrying >1 LQTS mutation (n=7) were excluded from the clinical characteristics (Table 1) and the multivariate model (Table 2), but included in the sections depicting cases of death and device therapy. The specific singular mutations included in the study, by number of patients, number of families, type, and location, are detailed in the Table 1 in the Data Supplement. Data on the 7 patients with >1 mutation in the KCNQ1 or KCNH2 genes are summarized in Table II in the Data Supplement. Noncarrier family members of the familial KCNQ1 and KCNH2 mutations served as the comparison group and are denoted as noncarrier relatives. All study subjects were of Finnish origin.12,14

Statistical Analysis

Clinical characteristics were compared using χ2 and Fisher’s exact tests for categorical, and Wilcoxon rank-sum and Kruskal–Wallis 1-way ANOVA tests for continuous variables. Categorical variables were expressed with number of patients and percentage, and continuous variables were expressed as mean±SD. Kaplan–Meier graphs were established to depict the cumulative probability (cumulative rate) of first cardiac event by mutation, QTc, and sex. The significance of the differences was tested by the log-rank test. LQT1 Finnish founder (FF) mutations KCNQ1 G589D and KCNQ1 c.1129-2A>G, and LQT2 FF mutations KCNH2 R176W and KCNH2 L552S were combined to form the FF mutation carrier population for LQT1 and LQT2, respectively.

Multivariate Cox proportional hazards regression model, comprising KCNQ1 and KCNH2 FF mutation, QTc duration categorized as ≥500, 470 to 499, or <470 ms, and time-dependent β-blocker medication as prespecified covariates, was used to evaluate the independent contribution of risk factors to first cardiac event in mutation carriers. The model was stratified by sex and adjusted for family membership using robust sandwich estimators. No violation of the proportional hazards assumption was detected as tested by log–log graphs. In an interaction term analysis, no statistically significant interactions were discovered, and thus no interaction terms were included in the multivariate model. A separate QTc missing covariate was used for patients whose baseline QTc data were not available (n=28).

The model stratified by sex and adjusted for family membership using robust sandwich estimators. No violation of the proportional hazards assumption was detected as tested by log–log graphs. In an interaction term analysis, no statistically significant interactions were discovered, and thus no interaction terms were included in the multivariate model.

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time from enrollment was 6.2±3.6 years, and the total follow-up time including the retrospectively collected data from birth was 12.0±5.5 years.

Clinical Characteristics

The characteristics of the study population are shown in Table 1 excluding patients with >1 mutation and noncarrier relatives. A baseline QTc ≥ 500 ms was measured in 32 (11%) individuals. There was no statistically significant difference in the age at which the first cardiac event occurred between LQT1 and LQT2 patients (6.8±4.4 and 8.9±4.6 years, respectively; \( P=0.24 \)). ACA or appropriate ICD shock was experienced by 0.9% of the LQT1 and 1.2% of the LQT2 patients. No SCDs occurred during the follow-up.

Risk Factors for Cardiac Events

As shown in Figure 1, the cumulative probability of cardiac events was higher in the carriers of non-FF than FF mutations by the age of 18 years (in \( KCNQ1 \) 26% versus 11%, \( P=0.008 \); and in \( KCNH2 \) 43% versus 4%, \( P=0.002 \)). Of the non-FF and FF mutation carriers, 2.7% and 0.4%, respectively (\( P=0.14 \)), had ACA or appropriate ICD shock. In \( KCNQ1 \) carriers, family history of ACA or SCD increased the risk of cardiac events (cumulative rate, 29% versus 13%; \( P=0.04 \)).

Table 1. Characteristics of the FF and Non-FF Mutation Carriers*

<table>
<thead>
<tr>
<th></th>
<th>( KCNQ1 )</th>
<th></th>
<th>( KCNH2 )</th>
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<tbody>
<tr>
<td></td>
<td>Non-FF†</td>
<td>FF</td>
<td>Non-FF†</td>
</tr>
<tr>
<td>n</td>
<td>n=42 (21%)</td>
<td>n=164 (72%)</td>
<td>n=32 (38%)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>19 (45)</td>
<td>85 (52)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Age at follow-up end, y, mean±SD</td>
<td>13.5±4.9</td>
<td>11.6±5.7</td>
<td>13.6±4.8</td>
</tr>
<tr>
<td>QTc, ms, mean±SD</td>
<td>475±43†</td>
<td>454±35</td>
<td>468±37†</td>
</tr>
<tr>
<td>QTc ≥700 ms, n (%)</td>
<td>20 (53)</td>
<td>43 (30)</td>
<td>16 (55)</td>
</tr>
<tr>
<td>( \beta )-Blocker, n (%)</td>
<td>36 (86)</td>
<td>138 (84)</td>
<td>28 (88)</td>
</tr>
<tr>
<td>Age at starting BB, y, mean±SD</td>
<td>4.3±5.1</td>
<td>5.1±5.4</td>
<td>7.2±5.4</td>
</tr>
<tr>
<td>Side effects, n (%)</td>
<td>9 (25)</td>
<td>29 (21)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Forgetting ≥ once a month, n (%)</td>
<td>9 (23)</td>
<td>33 (24)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>1 (2)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>4 (10)</td>
<td>1 (1)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>LCSD, n (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QT-related syncope, n (%)‌</td>
<td>9 (21)</td>
<td>11 (7)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>ACA, n (%)‡</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>SCD, n (%)#</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Age at first cardiac event, mean±SD</td>
<td>6.0±4.1</td>
<td>6.8±4.3</td>
<td>10±2.4</td>
</tr>
</tbody>
</table>

ACA indicates aborted cardiac arrest; BB, \( \beta \)-blocker; FF, Finnish founder; ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; LQTS, long-QT syndrome; and SCD, sudden cardiac death.

*Patients with >1 LQTS-causing mutation (n=7) are excluded.
†There was no statistical difference between \( KCNQ1 \) non-FF and \( KCNH2 \) non-FF mutation carriers in any of the parameters.
‡Significant \( P \) value (\( ≤0.05 \)) indicates that 1 group is different from the other 2 groups, or that all 3 groups differ from each other. Groups with different subscript letters (a, b, or c) have statistically significant difference.
§Trigger for the syncope was swimming, sport, loud noise, or startle. For 3 people, the data for syncope trigger were not available.
||A resuscitation that required external defibrillation or appropriate ICD shock.
#Not explained by any other cause and abrupt in onset if witnessed.

Table 2. Time-Dependent Cox Regression Model: Risk Factors for Cardiac Events in Mutation Carriers*

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( KCNQ1 ) FF vs ( KCNQ1 ) non-FF mutation</td>
<td>0.33</td>
<td>0.12–0.91</td>
<td>0.03</td>
</tr>
<tr>
<td>( KCNH2 ) FF vs ( KCNH2 ) non-FF mutation</td>
<td>0.16</td>
<td>0.04–0.66</td>
<td>0.01</td>
</tr>
<tr>
<td>QTc ≥500 vs &lt;470 ms</td>
<td>3.32</td>
<td>1.67–6.62</td>
<td>0.001</td>
</tr>
<tr>
<td>QTc ≥500 vs 470–499 ms</td>
<td>2.44</td>
<td>0.99–6.00</td>
<td>0.052</td>
</tr>
<tr>
<td>QTc 470–499 vs &lt;470 ms</td>
<td>1.36</td>
<td>0.49–3.76</td>
<td>0.55</td>
</tr>
<tr>
<td>( \beta )-Blocker vs no ( \beta )-blocker†</td>
<td>0.23</td>
<td>0.10–0.52</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The model was stratified by sex and adjusted for family membership using robust sandwich estimators. FF indicates Finnish founder.

*Patients with >1 long-QT syndrome–causing mutation (n=7) are excluded.
†Time-dependent covariate.
Non-FF LQT2 males had more cardiac events by the age of 10 years compared with non-FF LQT2 females (24% versus 0%; $P=0.05$; Figure 2). Thereafter, females had a distinct increase in events, and by the age of 18 years, the cumulative probabilities were 24% for men and 48% for women. Such a steep increase in risk in females was not observed among non-FF LQT1, FF LQT1, or FF LQT2 patients. Mutation carriers with QTc interval $\geq 500$ ms had a higher cardiac event rate (46%) than patients with QTc 470 to 499 ms (19%; $P=0.03$) or $<470$ ms (10%; $P<0.001$; Figure 3).

Vasovagal syncopes were equally common in LQTS patients and in noncarrier relatives (cumulative rate, 18% and 21%, respectively; $P=0.48$). Female noncarrier relatives had a steep increase in syncopal spells triggered by any reason after the age of 10, and by the age of 18 years, the rate was 41%. However, LQTS patients had significantly more cardiac events than their noncarrier relatives (male LQTS patients 12% versus noncarrier relatives 2%, $P=0.02$ and female LQTS patients 18% versus noncarrier relatives 4%, $P=0.007$).

Consistent with the findings of the Kaplan–Meier and log-rank analyses, in the Cox regression model, FF mutation carriers had a lower risk of cardiac events compared with non-FF mutation carriers (HR, 0.33; $P=0.03$ in $KCNQ1$ and HR, 0.16; $P=0.01$ in $KCNH2$; Table 2). QTc duration of $\geq 500$ ms was associated with a 3.3-fold risk of cardiac arrhythmia compared with QTc $<470$ ms ($P=0.001$), and a borderline significant 2.4-fold risk compared with QTc 470 to 499 ms ($P=0.052$). β-Blocker treatment was related to 77% reduction in the risk of first cardiac event ($P=0.001$). Cox regression model with only the firstborn patient from each of the 130 families was not feasible because of reduction in number of events.

### Medical Treatment

All patients received guidance on lifestyle modifications, such as avoidance of competitive sports, exposure to acoustic stimuli (LQT2), and QT-prolonging drugs, as recommended by the ACC/AHA/ESC guidelines.\(^6\) The only antiarrhythmic medication used was a β-blocker. More LQT1 than LQT2 patients were treated with β-blockers (86% versus 61%; $P<0.001$), and they started taking β-blocker earlier (4.9±5.3 versus 7.0±5.3 years; $P=0.02$). β-Blocker treatment was more common in $KCNH2$ non-FF than FF mutation carriers ($P<0.001$), but...
equally common in KCNQ1 non-FF and FF patients. All probands, all but 1 symptomatic patient, and 92% of patients with family history of ACA or SCD were treated with β-blockers. The 65 patients whom β-blocker was not prescribed had a shorter QTc interval (446 versus 461 ms; P=0.003), and they were less often symptomatic (2% versus 13%; P=0.01) than patients whom β-blocker was prescribed. There was no difference in age, female predominance, or family history of ACA or SCD between these 2 groups. None of the 49 nonproband mutation carriers with QTc <470 (434±21) ms, who were asymptomatic at enrollment and whom β-blocker was not initiated, had a cardiac event during the follow-up.

Propranolol was the most frequently (43%) prescribed β-blocker. Atenolol (26%) and bisoprolol (25%) were also used, whereas metoprolol was prescribed less often (6%). The dosage (mg/kg per day) was 2.4±0.8, 1.2±0.5, 0.1±0.1, and 1.3±0.4 for propranolol, atenolol, bisoprolol, and metoprolol, respectively. Only 15 subjects had a breakthrough cardiac event during β-blocker treatment. Supporting the findings of the multivariate Cox regression model, the incidence rate of cardiac events showed reduction after initiating β-blocker: in non-FF patients, 38.1 and 19.9 cardiac events per 1000 person-years before and after starting β-blocker, respectively. Similar trend was observed among FF patients (9.9 and 4.3 cardiac events per 1000 person-years).

Side effects were reported with similar frequency (22%–25%) in LQT1 and LQT2 patients. The most frequent side effects included nightmares and parasomnias (6%), coldness of extremities (6%), tiredness (6%), dizziness (4%), and impaired physical condition (4%). Furthermore, in 6 nondiabetic patients, β-blocker was suspected to aggravate hypoglycemia. Three of them were carriers of a single KCNQ1 mutation, 2 were homozygous carriers of the KCNH2 L552S mutation, and 1 was a double heterozygous carrier of KCNQ1 and KCNH2 mutations.

Side effects did not affect compliance to β-blocker medication. More LQT2 patients had difficulties in remembering to take the medicine than LQT1 patients (42% and 24%; P=0.02). Noncompliance to medication increased the risk of cardiac events in LQT2 patients; none of the compliant (n=29) but 18% (n=4) of the noncompliant patients had a cardiac event after initiating β-blocker medication (P=0.03). Such trend was not observed in LQT1 patients. A total of 8 LQT1 and 2 LQT2 patients with a mean QTc duration of 466 ms discontinued taking a β-blocker. The majority of them (7/10) carried a FF mutation. They were all asymptomatic at the time of discontinuation and remained cardiac event-free till the end of the follow-up. Only 1 patient, a KCNQ1 G589D mutation carrier with QTc duration of 470 ms, reported a side effect as the reason for discontinuation.

Device Therapy and LCSD

Characteristics of the patients with pacemaker, ICD, or LCSD are shown in Table 3.

Implantation indications for pacemakers included second-degree or third-degree atrioventricular block (n=3), neurocardiogenic syncope (n=2), and bradycardia (n=1). Implantation indications for ICDs were ACA or torsades de pointes (n=5), syncope despite β-blocker medication (n=2), and inadequate β-blocker compliance (n=2). ICD was implanted more frequently to non-FF than FF mutation carriers (10% and 0.4%; P<0.001). Two noncompliant patients (22%) under insufficient β-blocker medication received an appropriate ICD shock during the follow-up. None of the pacemaker or ICD patients were using QT-prolonging drugs at the time of cardiac event or ICD shock.

Pacemaker therapy complications (ie, inappropriate sensing and lead damage) were encountered in 2 patients. ICD therapy complications occurred in 4 (44%) patients: inappropriate ICD shocks because of lead damage (n=2), lead tension (n=1), and perforation of the right ventricle (n=1). All ICD complications resulted in lead replacement. The incidence rate of complications in pacemaker and ICD systems was 4.6 and 8.5 per 100 person-years, respectively.

LCSD was performed on 3 (1%) patients because of recurrent syncope: a β-blocker medication–compliant compound heterozygous KCNQ1 mutation carrier, a compliant homozygous KCNQ1 G589D mutation carrier, and a noncompliant KCNQ1 R366W mutation carrier. Two of them had a LQTS-related syncope after the procedure.

Causes of Death

A total of 3 patients died, but no SCDs occurred during the follow-up.
A 4-year-old nondiabetic boy with a double heterozygous KCNQ1 G589D and KCNH2 R176W mutation was the proband in the family. He had been examined for small size, delayed development of speech, and problems in eating. QTc was prolonged (460 ms) and propranolol was initiated. Six months later during respiratory infection and fever he lost consciousness, and severe hypoglycemia of 0.9 mmol/L was discovered. Intravenous glucose administration resulted in full recovery of consciousness. However, this was followed by aspiration of vomitus and a need of mechanical ventilation in the absence of ventricular tachyarrhythmias. Despite the intensive care, 2 days later, he was declared brain-dead.

Case 2
An 11-year-old symptomatic girl with KCNQ1 G589D mutation and QTc duration of 480 ms died because of an inoperable malignant temporal glioma.

Case 3
A nondiabetic girl who was homozygous for KCNH2 L552S mutation with a QTc time of 680 ms had recurrent 2:1 atrioventricular conduction block, R-on-T premature ventricular complexes, and short episodes of ventricular tachycardias since birth, and propranolol was initiated. At the age of 3 years, she was found unconscious with low (1.1 mmol/L) blood glucose level that was treated in hospital by rapid intravenous glucose administration. She regained consciousness, but after 15 minutes she vomited, aspirated, and went lifeless. Monitoring of heart rhythm showed no ventricular tachyarrhythmias. She died despite of cardiopulmonary resuscitation.

QTc Duration and Cardiac Events in Finnish Founder Mutation Carriers
All 4 FF mutations resulted in a significant QT prolongation compared with noncarrier relatives (451±35 versus 408±23 ms; P<0.001), but the QT-prolonging effect was weaker than that of non-FF mutations (Table 1). The cumulative probability of cardiac events by the age of 18 years was higher in FF mutation carriers than in noncarrier relatives (9% versus 3%; P<0.05). However, FF patients with QTc duration <470 ms had as many cardiac events as noncarrier relatives (6% and...
that QTc duration is one of the strongest predictors of cardiac events. This is in line with previous studies, which postulate the age of 10 years occurred only among non-FF but not in FF patients. Furthermore, the steep increase in risk in LQT2 females after the age of 10 years occurred only among non-FF but not in FF patients. Thus, in our study, the mean QTc interval was shorter among patients carrying any of the 4 FF mutations. No SCDs occurred during the follow-up.

Discussion
The present follow-up study focused on genetically confirmed pediatric LQT1 and LQT2 patients of Finnish origin and showed that, once treated with β-blockers and appropriate lifestyle modifications,10 the prognosis of the disorder is good. No SCDs occurred during the follow-up.

Risk Factors for Cardiac Events
In our study, non-FF LQT1 and LQT2 patients had cardiac events at a cumulative rate of 26% and 43%, respectively, similarly to the 30% to 45% reported in previous studies.5,19 ACAs, SCDs, and appropriate ICD shocks were less frequent (2.7% in non-FF patients) than in other studies 5% to 12%.2,6 However, in the previous studies >50% of the patients were diagnosed based on prolonged QTc time and history of syncope, whereas our study included only genetically confirmed LQTS patient irrespective of their QTc interval and syncope history. Thus, in our study, the mean QTc interval was shorter (458 versus 491–494 ms) reflecting a more benign phenotype.

In this study, the rate of cardiac events was considerably lower among patients carrying any of the 4 FF mutations. This is in accordance with previous observations suggesting that FF mutations lead to a milder clinical phenotype, even though all of them prolong the QTc interval, and have been shown to result in alterations of channel function in vitro.12,20,21 Furthermore, the steep increase in risk in LQT2 females after the age of 10 years occurred only among non-FF but not in FF patients.

In our study, a QTc interval of ≥500 ms was associated with a 3.3-fold risk of cardiac events compared with QTc <470 ms. This is in line with previous studies, which postulate that QTc duration is one of the strongest predictors of cardiac events.13 However, non-FF patients had an increased risk even with a normal QTc time (≤450 ms). Thus, other methods in patient risk stratification should be used along with QTc interval evaluation.22

The number of benign syncopal episodes in noncarrier female relatives increased after the age of 10 years, as described also in another study recently,15 complicating the differential diagnosis between LQTS-related and benign syncpe. However, 4 noncarrier relatives, with QTc interval <460 ms, had a syncpe triggered by sports, loud noise, or startle. When assessing an exercise-related syncopal spell, it is important to know whether the syncpe occurred during or immediately after cessation of physical effort. The latter is highly suggestive of a syncopal spell because of a sudden drop in blood pressure.

Medical Treatment
In this study, 79% of the children were on β-blocker medication in line with the pediatric study by Liu et al6 (72%). In the study by Etheridge et al17 as much as 98% of pediatric LQTS patients had β-blocker medication. However, in their study, the majority of the patients (53%) were diagnosed based on family history and prolonged QTc (mean 487 ms) suggesting a more severe phenotype compared with our study population. In our study, β-blocker medication was associated with a significant 77% reduction in cardiac events similarly to the previous studies.5–9,23 The result was supported by the reduction in the incidence rate of cardiac events. However, our hazard ratio estimate for the β-blocker treatment might be optimistic because we have only considered the first-ever cardiac events as the end point.

We showed that LQT2 patients had weaker adherence to β-blocker medication than LQT1 patients. Furthermore, noncompliant LQT2 patients had more cardiac events than compliant LQT2 patients. Patient guidance may play a role in compliance. LQT1 patients may be aware of the high efficacy of β-blockers in LQT1, and they may be more motivated to uninterrupted medication. Even though β-blockers may not be as effective in LQT2,24 they do prevent potentially fatal cardiac events also in this subtype.18,19,23 Therefore, it is important to pay attention to patient and parental motivation to ensure compliance.

Major potential complications of the β-blocker medication included hypoglycemia. In 2 cases, hypoglycemia was observed at the beginning of chain of events leading to death. In addition, 6 (2%) β-blocker users reported hypoglycemia as an adverse effect of the medication. Especially nonselective β-blockers are known to predispose young children to hypoglycemia by reducing glycolgenolysis and mobilization of glucose from the liver.25 β-blockers also attenuate hypoglycemic adrenergic symptoms.25,26 Thus, it is possible that β-blocker was a contributing factor to low blood glucose in the 2 cases of death in our study. Consequently, it is important to instruct pediatric LQTS patients and their parents about the risk of hypoglycemia as a potential side effect of β-blocker medication. Furthermore, Torekov et al27 reported recently that a loss-of-function mutation in KCNQ1 itself may cause hypoglycemia.

Device Therapy
In this study, only 3% of the total study population and 10% of the carriers of non-FF mutation received an ICD. This is less than the 15% reported in a previous study of device therapy on pediatric LQTS patients.7 However, in the previous study, 10% of the genetically tested subjects were carriers of an SCN5A mutation and all of them had an ICD implanted. LQT3 patients are known to respond poorly to the β-blocker medication and thus are more likely to receive an ICD even in primary prevention.10 Appropriate ICD shocks, inappropriate ICD discharges, and device reinterventions occurred in
similar rates as in previous studies. Although the sample size of device patients in our study was small, the occurrence of appropriate ICD shocks in 22% of the ICD patients underscores not only the importance of careful medical therapy but also of device therapy in patients lacking sufficient response to medication. However, high prevalence of complications and reinterventions (44%) in the present study does not support a more active approach to ICD implantation.

**Risk Stratification and β-Blocker Treatment**

Because of the lack of randomized trials, recommendations for LQTS management are based on expert opinion. The safety of β-blockers favors their use in pediatric LQTS patients because of the risk of arrhythmia later in adolescence. According to the prevailing treatment strategy among Finnish pediatric cardiologists, β-blocker should be initiated at the time of diagnosis to all patients who are either symptomatic, have QTc ≥470 ms, carry a KCNQ1 mutation, or carry a KCNH2 non-FF mutation. However, β-blocker may be initiated later but before the onset of adolescence to asymptomatic LQT2 FF patients with QTc time <470 ms if there is no family history of ACA or SCD. However, in the present study patients, to whom β-blocker medication was not prescribed, had an excellent cardiac event–free survival. This indicates that the current treatment strategy is adequate.

**Conclusions**

In the era of genetic screening, the number of detected asymptomatic LQTS mutation carriers is increasing. This study shows that life-threatening cardiac events are rare in molecularly defined and appropriately treated pediatric LQT1 and LQT2 patients. Thus, an active approach to genetic screening, larly defined and appropriately treated pediatric LQT1 and shows that life-threatening cardiac events are rare in molecu-


Follow-Up of 316 Molecularly Defined Pediatric Long-QT Syndrome Patients: Clinical Course, Treatments, and Side Effects

Mikael Koponen, Annukka Marjamaa, Anita Hiippala, Juha-Matti Happonen, Aki S. Havulinna, Veikko Salomaa, Annukka M. Lahtinen, Taina Hintsa, Matti Viitasalo, Lauri Toivonen, Kimmo Kontula and Heikki Swan

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### Supplemental Tables

#### Table 1S. Missense and nonmissense mutations in LQT1 and LQT2 patients.

<table>
<thead>
<tr>
<th>Codon/Type</th>
<th>n (%)</th>
<th>Families, n</th>
<th>Mutation type</th>
<th>Mutation location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FF-mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>KCNQ1</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.G589D</td>
<td>164 (73)</td>
<td>62</td>
<td>missense</td>
<td>C-terminus</td>
</tr>
<tr>
<td>c.1129-2A&gt;G</td>
<td>18 (8)</td>
<td>10</td>
<td>splice site</td>
<td>C-terminus</td>
</tr>
<tr>
<td><em>KCNH2</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.R176W</td>
<td>30 (35)</td>
<td>14</td>
<td>missense</td>
<td>N-terminus</td>
</tr>
<tr>
<td>p.L552S</td>
<td>23 (27)</td>
<td>11</td>
<td>missense</td>
<td>pore loop</td>
</tr>
<tr>
<td><strong>Non-FF mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>KCNQ1</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.D317N</td>
<td>11 (5)</td>
<td>1</td>
<td>missense</td>
<td>MS</td>
</tr>
<tr>
<td>p.R366W</td>
<td>8 (4)</td>
<td>3</td>
<td>missense</td>
<td>C-terminus</td>
</tr>
<tr>
<td>p.S277del</td>
<td>4 (2)</td>
<td>2</td>
<td>deletion</td>
<td>MS</td>
</tr>
<tr>
<td>p.A341V</td>
<td>3 (1)</td>
<td>1</td>
<td>missense</td>
<td>MS</td>
</tr>
<tr>
<td>p.G269S</td>
<td>3 (1)</td>
<td>1</td>
<td>missense</td>
<td>MS</td>
</tr>
<tr>
<td>p.R561G</td>
<td>3 (1)</td>
<td>1</td>
<td>missense</td>
<td>C-terminus</td>
</tr>
<tr>
<td>c.1032G&gt;A</td>
<td>2 (0.9)</td>
<td>1</td>
<td>splice site</td>
<td>MS</td>
</tr>
<tr>
<td>Gene</td>
<td>Variants</td>
<td>Frequency</td>
<td>Impact</td>
<td>Location</td>
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<td>------</td>
<td>----------</td>
<td>-----------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>p.S277L</td>
<td>2 (0.9)</td>
<td>missense</td>
<td>MS</td>
<td></td>
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<tr>
<td>p.W248C</td>
<td>2 (0.9)</td>
<td>missense</td>
<td>cytoplasmic loop</td>
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<tr>
<td>p.G325R</td>
<td>1 (0.4)</td>
<td>missense</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>p.R231C</td>
<td>1 (0.4)</td>
<td>missense</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>p.S546L</td>
<td>1 (0.4)</td>
<td>missense</td>
<td>C-terminus</td>
<td></td>
</tr>
<tr>
<td>p.T311I</td>
<td>1 (0.4)</td>
<td>missense</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>KCNH2</td>
<td>32 (38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.453delC</td>
<td>14 (16)</td>
<td>frameshift</td>
<td>N-terminus</td>
<td></td>
</tr>
<tr>
<td>c.1558-1G&gt;C</td>
<td>2 (2)</td>
<td>splice site</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>c.1631_1632delAG</td>
<td>2 (2)</td>
<td>frameshift</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>p.N629S</td>
<td>2 (2)</td>
<td>missense</td>
<td>pore loop</td>
<td></td>
</tr>
<tr>
<td>c.2654delG</td>
<td>1 (1)</td>
<td>frameshift</td>
<td>C-terminus</td>
<td></td>
</tr>
<tr>
<td>c.3092_3093insGCGGG</td>
<td>1 (1)</td>
<td>frameshift</td>
<td>C-terminus</td>
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</tr>
<tr>
<td>c.3093_3106del</td>
<td>1 (1)</td>
<td>frameshift</td>
<td>C-terminus</td>
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</tr>
<tr>
<td>c.853_859dupGCCGACG</td>
<td>1 (1)</td>
<td>frameshift</td>
<td>N-terminus</td>
<td></td>
</tr>
<tr>
<td>p.A561V</td>
<td>1 (1)</td>
<td>missense</td>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>p.C39Ter</td>
<td>1 (1)</td>
<td>nonsense</td>
<td>N-terminus</td>
<td></td>
</tr>
<tr>
<td>p.G572S</td>
<td>1 (1)</td>
<td>missense</td>
<td>pore loop</td>
<td></td>
</tr>
<tr>
<td>p.G584S</td>
<td>1 (1)</td>
<td>missense</td>
<td>pore loop</td>
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</tr>
<tr>
<td>p.P451L</td>
<td>1 (1)</td>
<td>missense</td>
<td>MS</td>
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<tr>
<td>p.R328C</td>
<td>1 (1)</td>
<td>missense</td>
<td>N-terminus</td>
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<tr>
<td>p.T613M</td>
<td>1</td>
<td>(1)</td>
<td>missense</td>
<td>pore loop</td>
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<tr>
<td>p.W497Ter</td>
<td>1</td>
<td>(1)</td>
<td>nonsense</td>
<td>MS</td>
</tr>
</tbody>
</table>

Reference sequences: NM_000218.2 (*KCNQ1*) and NM_000238.3 (*KCNH2*).

FF=Finnish founder, MS=membrane spanning.
Table 2S. Characteristics of the patients with >1 mutation in the *KCNQ1* or *KCNH2* genes.

<table>
<thead>
<tr>
<th>Case</th>
<th>Mutations</th>
<th>Female</th>
<th>QTc (ms)</th>
<th>Cardiac event*</th>
<th>β-blocker</th>
<th>Device therapy and LCSD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>KCNH2</em> p.L552S and <em>KCNH2</em> p.L552S</td>
<td>yes</td>
<td>513</td>
<td>ACA, ICD shock</td>
<td>yes</td>
<td>ICD (15.7)</td>
</tr>
<tr>
<td>2</td>
<td><em>KCNH2</em> p.L552S and <em>KCNH2</em> p.L552S</td>
<td>yes</td>
<td>636</td>
<td>no</td>
<td>yes</td>
<td>PM (0.1)</td>
</tr>
<tr>
<td>3‡</td>
<td><em>KCNH2</em> p.L552S and <em>KCNH2</em> p.L552S</td>
<td>yes</td>
<td>677</td>
<td>Syncope</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td><em>KCNQ1</em> p.G589D and <em>KCNH2</em> p.R176W</td>
<td>no</td>
<td>451</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>5‡</td>
<td><em>KCNQ1</em> p.G589D and <em>KCNH2</em> p.R176W</td>
<td>no</td>
<td>457</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>6§</td>
<td><em>KCNQ1</em> p.G589D and <em>KCNQ1</em> p.G589D</td>
<td>no</td>
<td>592</td>
<td>Syncope</td>
<td>yes</td>
<td>LCSD (5.8)</td>
</tr>
<tr>
<td>7§</td>
<td><em>KCNQ1</em> p.G589D and <em>KCNQ1</em> p.Y171Ter</td>
<td>no</td>
<td>566</td>
<td>Syncope</td>
<td>yes</td>
<td>PM (9.0), LCSD (11.7)</td>
</tr>
</tbody>
</table>

*Included LQTS-related syncope, ACA, appropriate ICD shock and SCD. The trigger for the syncope was swimming, sport, loud noise or startle.

†The age of ICD and pacemaker implantation, and LCSD in the parenthesis.
‡Both cases 3 and 5 died during the follow-up due to aspiration with hypoglycemia as a contributing cause of death.

§Cases 6 and 7: congenital deafness.

ACA=aborted cardiac arrest, ICD=implantable cardioverter-defibrillator, LCSD=left cardiac sympathetic denervation, ms=milliseconds, PM=pacemaker, SCD=sudden cardiac death.