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ORIGINAL ARTICLE

Risk Stratification of Type 2 Long-QT Syndrome Mutation Carriers With Normal QTc Interval

The Value of Sex, T-Wave Morphology, and Mutation Type

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BACKGROUND: Long-QT (LQT) syndrome mutation carriers have higher risk of cardiac events than unaffected family members even in the absence of QTc prolongation. Changes in T-wave morphology may reflect penetrance of LQT syndrome mutations. We aimed to assess whether T-wave morphology may improve risk stratification of LQT2 mutation carriers with normal QTc interval.

METHODS: LQT2 mutation carriers with QTc <460 ms in men and <470 ms in women (n=154) were compared with unaffected family members (n=1007). Baseline ECGs recorded at age ≥18 years underwent blinded assessment. Flat, notched, or negative T waves in leads II or V_5 were considered abnormal. Cox regression analysis was performed to assess the association between T-wave morphology, the presence of mutations in the pore region of *KCNH2*, and the risk of cardiac events defined as syncope, aborted cardiac arrest, defibrillator therapy, or sudden cardiac death. Sex-specific associations were estimated using interactions terms.

RESULTS: LQT2 female carriers with abnormal T-wave morphology had significantly higher risk of cardiac events compared with LQT2 female carriers with normal T waves (hazard ratio, 3.31; 95% confidence interval, 1.68–6.52; *P*=0.001), whereas this association was not significant in men. LQT2 men with pore location of mutations have significantly higher risk of cardiac events than those with nonpore mutations (hazard ratio, 6.01; 95% confidence interval, 1.50–24.08; *P*=0.011), whereas no such association was found in women.

CONCLUSIONS: The risk of cardiac events in LQT2 carriers with normal QTc is associated with abnormal T-wave morphology in women and pore location of mutation in men. The findings further indicate sex-specific differences in phenotype and genotype relationship in LQT2 patients.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: genotype ■ long-QT syndrome ■ mutation ■ risk ■ sex

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WHAT IS KNOWN?

- Genotype-positive patients with long-QT syndrome are at risk for cardiac events even if QTc durations do not exceed normal limits and β-blocker therapy is advocated for asymptomatic genotype-positive long-QT syndrome patients regardless of their QTc duration.
- Female sex is associated with higher risk of cardiac events in patients with long-QT syndrome.
- Disease-causing mutation penetrance may be manifested in both QTc prolongation and alterations of T-wave morphology.

WHAT THE STUDY ADDS?

- Among adult LQT2 mutation carriers with normal QTc, further risk stratification is possible using sex, T-wave morphology, and mutation localization within the *KCNH2* gene.
- Women patients with LQT2 remain to be at higher risk of cardiac events than men even in the normal range QTc, whereas men patients do not demonstrate risk increase compared with control population.
- Performance of electrocardiographic and genetic risk indicators is sex specific and can be used for patient-tailored risk stratification and β-blocker use.

Introduction of cascade genetic screening in the management of families with long-QT syndrome (LQTS) has led to the identification of the growing number of mutation carriers, many of whom have normal QTc. Earlier studies indicated that mutation carriers have higher risk of cardiac events than genotype-negative family members even in the absence of QTc prolongation,[1] which is used as a rationale for administration of β-blocker therapy to asymptomatic LQTS mutation carriers regardless of QTc duration.[2] Mutation penetrance, however, may be manifested not only in QTc prolongation but also in aberrant T-wave morphology with most notable T-wave abnormalities associated with LQT2 genotype.

The type and location of LQT2 mutation seem to be associated with the risk of cardiac events with the highest risk confined to pore mutations as reported in a large international LQT2 cohort.[3] However, it is not known whether the risk conferred by a specific mutation type is independent of repolarization abnormalities detectable as either prolonged QTc or abnormal T-wave morphology in *KCNH2* mutation carriers. In an earlier study that included patients with all 3 most common LQTS genotypes, the impact of the mutation type (ie, transmembrane missense mutations) was confined only to the mutations carriers who did not exhibit QTc prolongation, whereas in patients with prolonged QTc, the predictive effect of the genotype was attenuated.[1]

We hypothesized that LQTS penetrance in LQT2 mutations carriers with normal QTc interval assessed as occurrence of arrhythmic events and syncopal episodes is linked to the type of *KCNH2* mutation and T-wave morphology alterations that can be assessed from standard resting ECG. Our aim was to assess whether abnormal T-wave morphology and information on location of the genetic defect may be useful in risk stratification of adult LQT2 mutation carriers with normal QTc interval in the Rochester LQTS Registry.

MATERIALS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

Patients in this study were from the Rochester-based LQTS Registry; enrollment into the registry has been previously described.[4,5] Patients were selected to the current analysis if they (1) were shown to be carriers of disease-causing mutation in *KCNH2* (LQT2), (2) had Bazett-corrected QT interval (QTc) <470 ms for women and <460 ms for men, and (3) were 18 years or older to exclude variation of T-wave morphology that may be observed in children and adolescents. Patients were excluded from the study if they had >1 LQTS-associated mutation.

The study population selected according to these criteria comprised 154 subjects with genotype-positive LQT2 patients and normal or minimally affected QTc and subjects belonging to families with genotype-positive probands who were genetically tested and found to be negative for LQTS-associated mutation (n=1007).

Data Collection

Standard 12-lead resting ECG was acquired at the time of enrollment in the registry. RR and QT intervals were measured on the first recorded ECG and used for calculation of the heart rate–corrected QT interval according to the Bazett formula (QTc). Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, therapies, including QT-prolonging medications, and events during long-term follow-up. Information about β-blocker use was also collected to allow time-dependent assessment of their possible impact on the incidence of cardiac events.

End Points

The prespecified end point of the study was the occurrence of a first cardiac event (CE) that included syncope (defined as transient loss of consciousness that was abrupt in onset and recovery), aborted cardiac arrest (ACA) requiring defibrillation as a part of resuscitation attempts, 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 including sleep).

ECG-Phenotype Characterization

All incoming ECGs were assessed by a cardiologist (W.Z.) blinded to subjects' clinical characteristics in regard to the T-wave morphology in leads V_5 and II, which was classified as either normal, broad, flat, notched, negative, or biphasic.[6,7] For the purpose of this analysis, T-wave morphologies, which were not assessed as normal in either lead II or V_5, were classified as abnormal, indicating the possible presence of ventricular repolarization abnormality/mutation penetrance.

ECGs were also assessed in regard to the conventional interval measurements such as PR, QRS, QT measured in the limb lead II and corrected using Bazett formula, and Tpeak–Tend interval measured from the absolute maximum of the T wave to the end of the QT interval.

The study was approved by an institutional review board and study participants provided informed consent.

Genotype Characterization

The presence of LQTS-causing *KCNH2* mutation was verified with the use of standard genetic tests performed in academic molecular genetic laboratories reported previously.[1] Genetic alterations of the amino acid sequence were characterized by location in the channel protein, which was defined as belonging to the pore region if the coding sequence involved amino acid residues located in the S5-loop-S6 region (552 through 657). All other genetic variants were considered as nonpore mutations for the purpose of this study.

Statistical Analysis

Differences in the univariate characteristics by LQT2-normal QTc subjects versus genotype-negative control subjects were compared using the χ^2 test or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Categorical data were presented as frequency and percentage and continuous variables as mean±SD or median and corresponding interquartile range.

The cumulative probability of the primary and secondary end points was assessed by the Kaplan-Meier method with significance testing by the log-rank statistic. The Cox proportional hazard model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of time-dependent cardiac events from the age of 18 years through the end of follow-up. The Cox regression model was adjusted for the time-dependent β-blocker use (the age at which patients were on and off β-blocker therapy) and stratified by sex. As preselected QTc inclusion criteria overlapped with borderline QTc prolongation, the model was also adjusted for QTc duration with 440 ms selected as a cutoff for normal versus borderline QTc values. To develop sex-specific regression parameter estimates for the clinical and genetic factors, interactions between sex and the variables of interest were used. The proportionality assumption was tested using time-dependent covariates created from interactions between survival time and various covariates.

All statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

Distribution of QTc intervals in the study group and genotype-negative control group are presented in Figure 1. In total, 60 unique pathogenic genetic variants were reported among normal QTc mutation carriers, of whom the vast majority (n=119, 78%) carried mutations that were also reported among affected family members with prolonged QTc.

The clinical characteristics of the study population are presented in Table 1 with comparisons between normal QTc LQT2 carriers and noncarriers. The age at enrollment in the registry and sex distribution did not differ between the groups. There were differences in QTc duration which was longer in carriers than noncarriers despite being within normal limits. Tpeak–Tend measured in leads II and V_5 was also longer in mutation carriers. Abnormal T-wave morphology was observed in 39% of LQT2 carriers with normal QTc and in 7% noncarriers. The pore mutations were identified in 15% of carriers. Syncope before the age of 18 years was observed in 23 LQT2 carriers with normal QTc, of whom 5 had pore mutations and 12 had abnormal T-wave morphology.

Among the 154 LQT2 carriers, there were 44 (29%) patients with cardiac events ≥18 years of age including 8 (5%) ACA or SCD. Out of the 1007 noncarriers, 135 (13%) patients had at least 1 cardiac event including 3 (0.3%) with ACA or SCD. Because of small number of ACA/SCD in this cohort, we focused our analyses on cardiac events. Of the 25 implantable cardioverter-defibrillator recipients among LQT2 carriers none had prior history of cardiac arrest or documented torsades de pointes; however, 9 had a history of syncope and 6 had family history of SCD. A single individual from this group who received an implantable cardioverter-defibrillator discharge during follow-up was a carrier of nonpore mutation 209 A>G, had abnormal T-wave morphology, and a baseline QTc of 450 ms.

Clinical Course in the LQT2 Carriers With Normal QTc

T-Wave Morphology

Figure 2A shows cumulative probability of cardiac events in LQT2 carriers with abnormal T wave versus LQT2 carriers with normal T wave in comparison to noncarriers. After

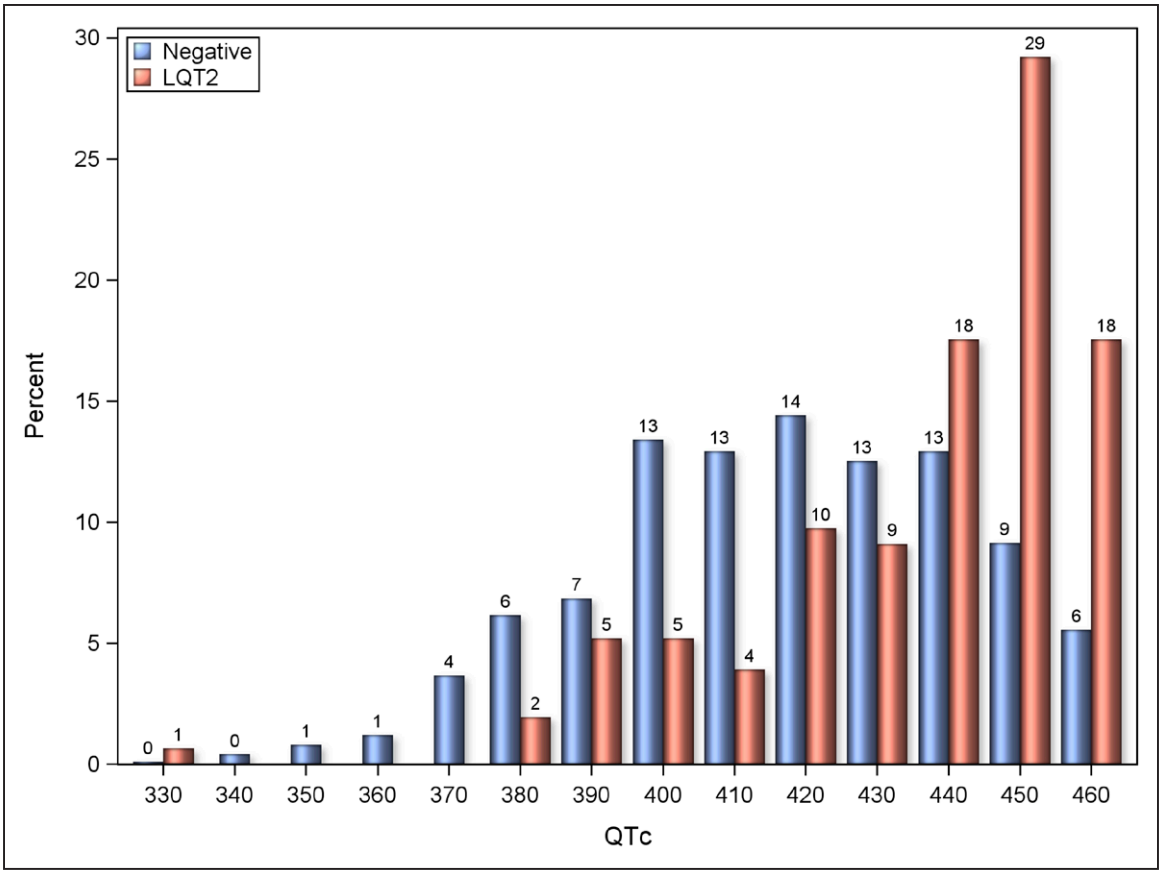

Figure 1. QTc distribution histogram for type 2 long-QT (LQT2) patients with normal QTc and genotype-negative control subjects.

10 years of follow-up from the age of 18 years old, LQT2 carriers with abnormal T wave had significantly higher rate of cardiac events than LQT2 carriers with normal T wave and noncarriers (27% versus 10% and 6% respectively; *P*<0.001). After 30 years of follow-up from the age of 18 years, the rates were 37% versus 19% (*P*=0.134) and 12% (*P*<0.001), respectively. After multivariate adjustment for sex and time-dependent β-blocker therapy, LQT2 carriers with normal QTc and abnormal T-wave morphology had greater risk of cardiac events than LQT2 carriers with normal T-wave morphology and noncarriers (Table 2). In comparison with noncarriers, LQT2 carriers with normal T-wave morphology had a trend toward greater risk of cardiac events with hazard ratio (HR) of 1.58 (*P*=0.072). Tpeak–Tend did not demonstrate an independent prognostic value in the multivariable analysis, and its inclusion in the model did not affect the results.

Pore Versus Nonpore LQT2 Mutation

Carrying LQT2 mutation in the pore domain appeared to be a risk indicator in the subgroup of mutation-positive patients with normal QTc (Figure 2B). After multivariate adjustment for sex and time-dependent β-blocker therapy, normal QTc LQT2 carriers with pore mutations had a trend toward greater risk of cardiac events than nonpore LQT2 mutations carriers (HR, 1.93; *P*=0.068; Table 2).

We have also performed a sensitivity analysis by excluding normal QTc LQT2-mutation carriers who had syncopal episodes before the age of 18 years, which yielded similar Kaplan-Meier curve analysis results and did not affect risk estimates.

Sex-Related Risk of Cardiac Events in LQT2 Mutation Carriers

Because the risk of cardiac events is significantly different in adult LQT2 women than men, we analyzed the above associations in men and women separately (Table 3). Among LQT2 carriers with normal QTc, women had greater risk of cardiac events than men (HR, 4.09, 95% confidence interval, 1.89–8.81; *P*<0.001; Figure 3).

Abnormal T-wave morphology was observed in 26 men (39%) and 29 women (33%); however, cardiac events were reported in only 4 (15%) men and 19 (66%) women (*P* value for interaction=0.018). As shown in Table 3, female LQT2 carriers with abnormal T wave had greater risk of cardiac events than female LQT2 carriers with normal T-wave morphology (HR, 3.31; *P*=0.001; Figure 4A and 4B). There was no significant association between T-wave morphology and cardiac events in men.

Table 1. Clinical Characteristics of the LQT2 Mutation Carriers With Normal QTc and Genotype-Negative Family Members

Clinical Characteristics	No. of Missing Values	LQT2 Normal QTc	No. of Missing Values	Genotype-Negative Controls	*P* Value
Number		154		1007	
Male, n (%)	0	67 (44)	0	414 (41)	0.574
Age at ECG, y	0	41±15	0	41±15	0.837
Pore mutation	1	23 (15)	0	0	…
Syncope <18 y, n (%)	0	23 (15)	0	62 (6)	<0.001
Electrocardiography					
RR, ms	0	959±174	0	893±166	<0.001
PR, ms	1	160±23	32	161±28	0.320
QRS, ms	0	84±14	0	85±14	0.438
QTc, ms	0	436±23	0	417±26	<0.001
Tpeak–Tend lead II, ms	4	94±31	3	86±21	0.004
Abnormal T-wave in V_5 or II	12	55 (39)	61	64 (7)	<0.001
Treatment					
β-Blockers	0	81 (53)	0	187 (19)	<0.001
ICD	0	25 (16)	0	17 (2)	<0.001
Cardiac events ≥18 y					
Syncope	0	41 (27)	0	133 (13)	<0.001
ACA	0	4 (3)	0	3 (0)	0.008
SCD	0	5 (3)	0	0 (0)	<0.001
Appropriate ICD shock	0	1 (1)	0	4 (0)	0.510

Data are presented as mean±SD or n (%). ACA indicates aborted cardiac arrest; ICD, implantable cardioverter-defibrillator; LQT, long QT; and SCD, sudden cardiac death.

Pore location of LQT2 mutations indicated significantly increased risk of cardiac events than in nonpore LQT2 mutation men (HR, 3.70; *P*=0.002). However, there was no such association in women (HR, 1.37; *P*=0.487; Figure 4C and 4D). LQT2 pore mutation carriers constituted the only men subgroup that demonstrated significant hazard compared with noncarriers (Figure 4C).

DISCUSSION

We have shown that among carriers of disease-causing mutations in the *KCNH2* gene with normal QTc interval further risk stratification can be achieved by combining information about patient sex, the affected *KCNH2* region, and T-wave morphology. Our findings extend earlier reported hazard associated with female sex to the subgroup of LQT2 mutation carriers with normal QTc interval. Furthermore, patients with normal T-wave morphology and nonpore *KCNH2* mutations generally have low risk of cardiac events; however, important differences in risk stratification value of these characteristics exist between men and women. Women carrying LQT2 mutations demonstrate significantly increased risk of cardiac events compared with genotype-negative controls, which is linked to the presence of abnormal T waves and not related to the type of mutation. On the contrary, carrying pore mutation was the only risk factor that identified a subgroup with elevated risk of CE among men.

Carriers of LQTS-causing mutations with normal QTc represent a challenging patient group. Though the risk of ACA/SCD is thought to be low, as shown by our group previously,[1] it still accounts for ≈4% cumulative risk by the age of 40 years and is 10-fold increased compared with unaffected family members. This observation has led to recommendation of β-blocker therapy in all LQTS mutation carriers regardless of QTc duration.[2] Even though β-blockers are known for their excellent safety profile, family members diagnosed as a result of

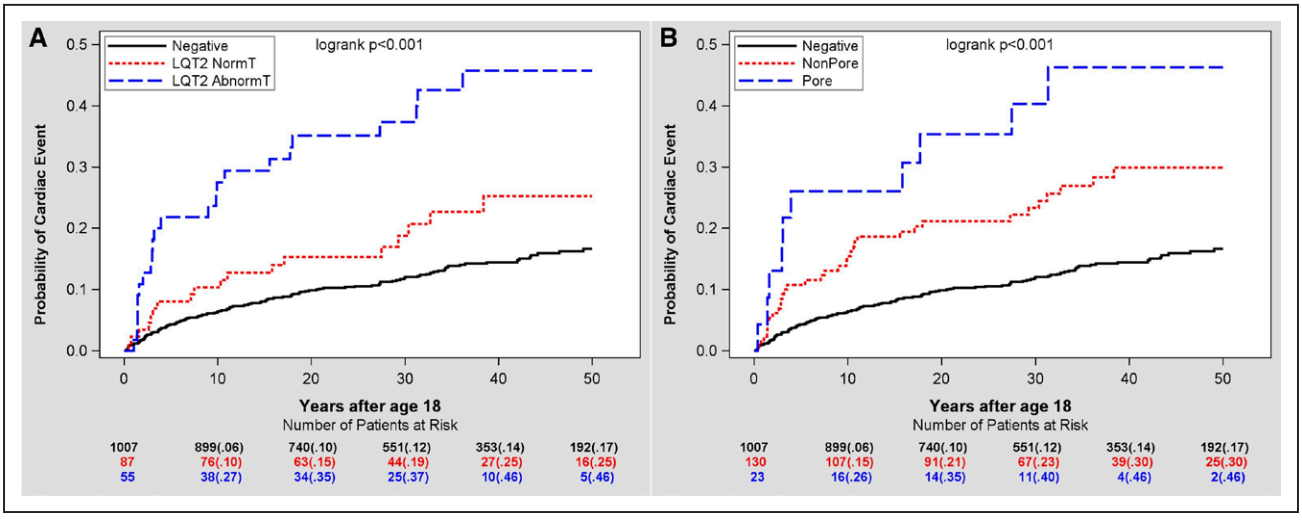

Figure 2. Risk of cardiac events in relation to the T-wave morphology and KCNH2 mutation type.
Kaplan-Meier curve analysis of the risk of cardiac events in relationship to the T wave morphology (**left**) or type 2 long-QT (LQT2) mutation type (**right**) in LQT2 mutation carriers with normal QTc compared with genotype-negative family members.

Table 2. Multivariable Analysis: Risk of Cardiac Events Among LQT2-Mutation Carriers With Normal QTc Interval and Genotype-Negative Unaffected Family Members (Adjusted for Sex, QTc, and Time-Dependent β-Blocker Therapy)

	Cardiac Events			
		95% CI		
	HR	Lower	Upper	*P* Value
T-wave morphology				
Abnormal vs normal T-wave LQT2	2.63	1.41	4.89	0.002
Abnormal T-wave LQT2 vs genotype negative	4.14	2.63	6.50	<0.001
Normal T-wave LQT2 vs genotype negative	1.58	0.96	2.58	0.072
LQT2 mutation type				
Pore vs nonpore	1.93	0.95	3.92	0.068
Pore vs genotype-negative controls	4.01	2.09	7.66	<0.001
Nonpore vs genotype-negative controls	2.07	1.42	3.03	<0.001

CI indicates confidence interval; HR, hazard ratio; and LQT, long QT.

widely implemented cascade genetic family screening are often young and healthy individuals, who are being exposed to a long-term β- blocker therapy and their associated side effects, which may significantly affect their quality of life. Further attempts to risk stratify

Table 3. Sex-Specific Estimates of the Risk of Cardiac Events Among Normal QTc LQT2 Carriers in Relationship to the T-Wave Morphology and Mutation Type (Adjusted for QTc and Time-Dependent β-Blocker Therapy)

	Women			Men		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
T-wave morphology						
Abnormal T wave vs genotype negative	6.01*	3.65–9.89	<0.001	1.52*	0.54–4.27	0.427
Normal T wave vs genotype negative	1.82	1.05–3.14	0.032	0.94	0.29–3.06	0.918
Abnormal vs normal T wave	3.31	1.68–6.52	0.001	1.58	0.35–7.07	0.549
Mutation type						
Pore vs genotype-negative	3.70	1.62–8.47	0.002	4.39	1.56–12.37	0.005
Nonpore vs genotype-negative	2.71†	1.79–4.09	<0.001	0.73†	0.26–2.05	0.549
Pore vs nonpore	1.37	0.57–3.29	0.487	6.01	1.50–24.08	0.011

CI indicates confidence interval; HR, hazard ratio; and LQT, long QT.
**P* value for interaction 0.018.
†*P* value for interaction 0.020.

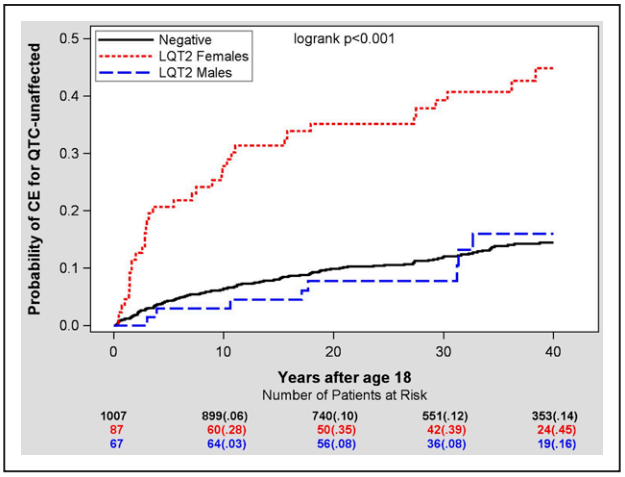

Figure 3. Kaplan-Meier curve analysis of cardiac events risk in type 2 long-QT (LQT2) male and female carriers compared with genotype-negative family members.

LQTS mutations carriers with normal QTc are therefore needed.

We hypothesized that mutation penetrance and associated arrhythmic risk may be assessed not only by the degree of QTc prolongation but also by the alterations in T-wave shape visible also in the normal QTc range. Among the 2 most common LQTS genetic variants, the type 2 is known for its characteristic T-wave distortion first described in 1995[6] and could be reliably distinguished by computer-based methods.[8–10] Our findings of strong association between the cardiologist-adjudicated abnormal T-wave morphology and the risk of arrhythmic events among patients with type 2 LQTS syndrome indicate that previously used terminology of phenotype-negative LQTS based exclusively on QTc assessment should be redefined and, at least in the context of type 2 LQTS, be based on assessment of both QTc and the shape of T wave.

Despite demonstrating lower risk of arrhythmic events compared with patients with abnormal T-wave morphologies, LQT2 women with normal T waves still had increased risk of cardiac events compared with genotype-negative family members, which was not observed among men. Significant residual risk observed among women with normal T waves may be because of the well-recognized impact of sex hormones on arrhythmogenesis reviewed recently,[11] which may not be directly translated in the abnormalities on surface ECG. However, it is also possible that the link between individual genetic variants and their expression on surface ECG is mutation specific and the arrhythmic risk may not be bound to the ECG expression of ion channel defect.

Association between mutations in the transmembrane pore region of *KCNH2* and increased arrhythmia risk was first reported in 2002[12] and later expanded in a large international cohort of LQT2 patients.[3] In line

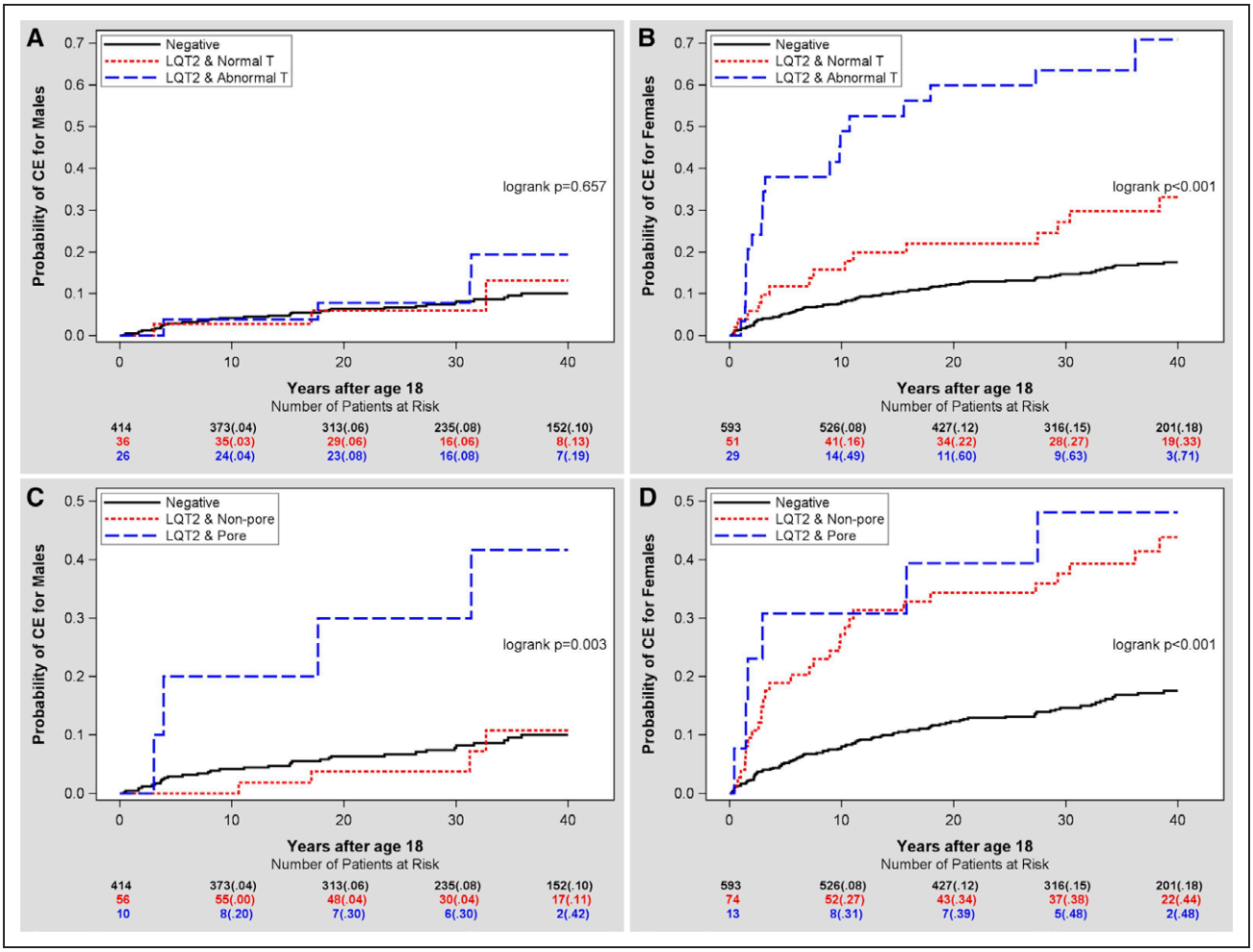

Figure 4. Gender-specific relationships between the T-wave morphology, KCNH2 mutation type, and the risk of cardiac events.
Kaplan-Meier curve analysis of cardiac events in relationship to the presence of the abnormal T-wave morphology (**A** and **B**) or transmembrane pore KCNH2 mutation (**C** and **D**) in normal QTc long type 2 long-QT (LQT2) mutation carriers compared with genotype-negative family members presented separately for men and women.

with earlier observations,[2] the prevalence of the pore mutations in our study was relatively low in our group of patients with normal QTc. In a previous analysis of the impact of mutation-specific characteristics on the outcome in patients with different variants of LQTS,[3] it was suggested that mutation characteristics had prognostic impact only among those with normal QTc interval, whereas in patients with prolonged QTc, it was the degree of QTc prolongation rather than the mutation type that affected the risk of arrhythmias. It is remarkable, however, that even low-risk nonpore mutations in our study were associated with 3-fold increased risk of cardiac events in LQT2 mutation male carriers with normal QTc compared with genotype-negative family members.

Our findings further illustrate the importance of sex in the risk assessment of LQT2 mutation carriers. Although female sex association with elevated risk of CE in LQT2 has been repeatedly reported earlier,[5,13] our findings extend this knowledge to the growing group of phenotype-negative mutation-carrying family members resulting from implementation of genetic cascade screening in the clinical routine. Even though T-wave morphology assessment could be useful in identifying the highest risk group in women, even LQT2 mutation–carrying women with ostensibly normal ECG, that is, normal T waves and normal QTc, seem to be at significantly elevated risk compared with noncarriers. Furthermore, the risk of CE associated with LQTS genotype persists through the lifetime as our group has shown previously,[14] and our current findings confirm the validity of this observation in women with normal QTc, who remain at risk through the late postmenopausal period. On the contrary, men carrying LQT2 mutations seem to be at a very low risk of events if they have normal QTc independently from T-wave morphology so that their risk of events remains undistinguishable from the genotype-negative controls with exception for the small minority of male subjects carrying pore mutations who had 4-fold risk increase compared with noncarriers.

Finally, our findings raise questions whether primary preventive β-blocker therapy, which is currently advo-

cated in mutation carriers with normal QTc,[2] should be applied indiscriminately. Our findings of sex-related differences on the risk of cardiac events among LQT2 mutation carriers with normal QTc suggest that men carrying a nonpore LQT2 mutation, which stands for the vast majority of male mutation carriers, are at the risk of arrhythmic events that is not distinguishable from the 1 observed in genotype-negative family members and thus may not have sufficient risk-benefit ratio for justifying lifelong β-blocker therapy.

Study Limitations

Our findings are only applicable to adult LQT2 mutation carriers because we have intentionally excluded individuals under 18 years of age because of a greater variation of age-related normal variants of T-wave morphology. It remains therefore unproven whether similar risk stratification scheme could be developed for children and infants born with disease-causing *KCNH2* variant and should be treated with β blockade according to the current recommendations.[2]

T-wave morphology adjudication was performed without use of automatic computer-based algorithms and therefore might have underestimated ECG manifestations of potassium channel malfunction possibly attributable to the arrhythmic risk in patients with normal T-wave morphologies.

Finally, even though the model was adjusted for time-dependent β-blocker use, we have not been able to access the information about circumstances surrounding reported CE. Therefore, we cannot account for possible triggers, exposure to potential QT-prolonging drugs or predisposing factors, which may have contributed to syncopal episodes in LQT2 mutation carriers.

Conclusions

Among electrocardiographically unaffected LQT2 patients, female sex, the T-wave morphology, and the type of LQT2 mutations are independently associated with the risk of cardiac events and should be considered in weighing risks and benefits of primary preventive therapies. Genotype-positive women LQT2 patients with normal QTc are at higher risk for cardiac events than control population, although the presence of T-wave abnormality is associated with a higher risk than normal T-wave morphology. Mutation type is useful in risk-stratifying cardiac events in men LQT2 carriers with normal QTc: nonpore LQT2 mutations are not at significantly different risk of cardiac events than unaffected family members. The findings indicate that risk stratification within the unaffected LQT2 mutation carriers is possible and advocate patient-tailored use of prophylactic β-blocker therapy.

ARTICLE INFORMATION

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Disclosures

None.

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