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Modulating Effects of Age and Gender on the Clinical Course of Long QT Syndrome by Genotype

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OBJECTIVES We aimed to determine whether long QT syndrome (LQTS) genotype has a differential effect on clinical course of disease in male and female children and adults after adjustment for QTc duration.

BACKGROUND Genotype influences clinical course of the LQTS; however, data on the effect of age and gender on this association are limited.

METHODS The LQTS genotype, QTc duration, and follow-up were determined in 243 cases of LQTS caused by the KCNQ1 potassium channel gene mutations (LQT1), 209 cases of LQTS caused by the HERG potassium channel gene mutations (LQT2), and 81 cases of LQTS caused by the SCN5A sodium channel gene mutation (LQT3) gene carriers. The probability of cardiac events (syncope, aborted cardiac arrest, or sudden death) was analyzed by genotype, gender, and age (children ≤ 15 years and adults 16 to 40 years). In addition, the risk of sudden death and lethality of cardiac events were evaluated in 1,075 LQT1, 976 LQT2, and 324 LQT3 family members from families with known genotype.

RESULTS During childhood, the risk of cardiac events was significantly higher in LQT1 males than in LQT1 females (hazard ratio [HR] = 1.72), whereas there was no significant gender-related difference in the risk of cardiac events among LQT2 and LQT3 carriers. During adulthood, LQT2 females (HR = 3.71) and LQT1 females (HR = 3.35) had a significantly higher risk of cardiac events than respective males. The lethality of cardiac events was highest in LQT3 males and females (19% and 18%), and higher in LQT1 and LQT2 males (5% and 6%) than in LQT1 and LQT2 females (2% for both).

CONCLUSIONS Age and gender have different, genotype-specific modulating effects on the probability of cardiac events and electrocardiographic presentation in LQT1 and LQT2 patients. (J Am Coll Cardiol 2003;42:103–9) © 2003 by the American College of Cardiology Foundation

The long QT syndrome (LQTS) is a familial disorder characterized by prolonged ventricular repolarization and a propensity for torsades de pointes leading to syncope and sudden death (1–3). Mutations in genes encoding potassium and sodium cardiac ion channel genes have been found to cause distinct forms of LQTS (4–6). The clinical course of LQTS is influenced by genotype (6,7). The LQT1 patients, carrying KCNQ1 potassium channel (IKs) gene mutation, and LQT2 patients, with HERG potassium channel (IKr) gene mutation, have a higher risk of cardiac events occurring throughout their lifetime than LQT3 patients carrying the SCN5A sodium channel (INa) gene mutation (6). However, LQT3 patients have a higher lethality of cardiac events than LQT1 and LQT2 patients (6). Our previous observations (8,9) also indicated that cardiac events tend to occur more frequently in childhood (age <16 years) with LQTS males having a higher risk and earlier onset of events than females. In adulthood (age 16 to 40 years), although the risk of cardiac events is decreasing, there is a gender-related difference: female LQTS patients experience more events than males (8,9). Age- and gender-related differences in QTc duration have been observed both in healthy subjects (10) and in LQTS patients (11); LQTS genotype has also been shown to influence QT interval duration and repolarization (T-wave) morphology (11–13). The above observations indicate that a complex relationship between genotype, age, gender, and QTc duration may influence the clinical course of the disease in LQTS patients, with possible modulating effects of age and gender on gene-specific clinical presentation. Our initial efforts to investigate this complex age-gender-genotype relationship were limited by the relatively small number of genotyped individuals (6,9). Presently, we have greatly expanded the patient cohort, which allows us to investigate whether

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Abbreviations and Acronyms

HR = hazard ratio
IKr = HERG potassium channel
IKs = KCNQ1 potassium channel
INa = SCN5A sodium channel
LQTS = long QT syndrome
LQT1 = long QT syndrome caused by the KCNQ1 potassium channel gene mutations
LQT2 = long QT syndrome caused by the HERG potassium channel gene mutations
LQT3 = long QT syndrome caused by the SCN5A sodium channel gene mutation

LQTS genotype has a differential effect on the clinical course of disease in male and female children, and adults, after adjustment for QTc duration.

METHODS

Study population. The study population described in this paper is an outgrowth of ongoing data collection by the International Long QT Syndrome Registry (1). The LQTS genotype was determined in 533 patients: 243 LQT1 gene carriers with the KCNQ1 mutations from 53 families, 209 LQT2 gene carriers with the HERG mutations from 61 families, and 81 LQT3 gene carriers with the SCN5A mutations from 9 families. Table 1 shows the breakdown of studied patients by genotype, gender, and age at last follow-up before cardiac event or initiation of beta-blocker treatment. The initiation of beta-blocker therapy was used as a censoring point to enable the analysis of the natural course of LQTS, that is, without influence of beta-blockers. The effectiveness of beta-blockers in LQTS was recently evaluated by our group (14) and, therefore, is not the subject of this analysis. The choice of age categories (children from 0 to ≤15 years and adults from 16 to 40 years) was based on our previous observation that risk of cardiac events may change after age 15 years (8,9). When analyzing the risk of cardiac events in children, all gene carriers with known QTc measurements and follow-up counted until age ≤15 were included. When evaluating the risk of cardiac events in adults, all LQTS gene carriers with recorded electrocardiograms (ECGs) who survived to age 16 without cardiac event and without beta-blocker treatment were included. Therefore, the children's group included all studied carriers, whereas in the adult group, carriers with cardiac events or beta-blocker treatment before 16 were excluded.

In addition to gene carriers, we also evaluated cardiac events in all directly related family members of genotyped LQTS carriers (without requiring a recorded ECG or genotyping) to determine the risk of sudden death and lethality of cardiac events, unbiased by QTc duration or access to genetic testing. Directly related family members were defined as those family members who were on the side of a family tree where LQTS was genetically confirmed, for example, in the case of disease inherited from the mother, only the maternal part of a family was included in the analysis. There were 1,075 such family members (including 243 carriers) from LQT1 families, 976 family members (including 209 carriers) from LQT2 families, and 324 family members (including 81 carriers) from LQT3 families.

ECG parameters. The first recorded ECGs (regardless of age) were routinely used to determine heart rate and the Bazett-corrected QTc interval. Because in two-thirds of carriers the first ECG was recorded after age 15, we analyzed QTc duration by genotype and gender, using ECGs recorded at age 0 to ≤15 and 16 to 40 years separately. This analysis was also performed while excluding probands, to diminish potential bias introduced by the definition of probands (requiring QTc > 440 ms).

Cardiac events. Cardiac events were defined as syncope, aborted cardiac arrest (requiring defibrillation), or sudden cardiac death, whichever occurred first. Cardiac events occurring before initiation of beta-blocker therapy were considered as the primary end point to avoid confounding influence of these drugs on the probability of cardiac events. The analysis of first cardiac event as an end point, regardless of beta-blocker use, was also performed. To limit the potential confounding effect of coronary artery disease on the outcome of studied patients, only cardiac events occurring by age 40 years were considered. In addition, we analyzed the risk of recurrent cardiac events (at least two cardiac events) and cardiac event rates per patient per year in studied LQTS carriers.

In family members, we compared the occurrence of death in males versus females by genotype and gender in age-

Table 1. Number and Follow-Up of LQTS Gene Carriers by Gender and Age*

	LQT1		LQT2		LQT3	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**
Age ≤15 yrs						
Number of carriers	108	135	88	121	42	39
Mean ± SD follow-up (yrs)*	12 ± 5	14 ± 4	13 ± 5	14 ± 4	13 ± 5	13 ± 5
Age 16–40 yrs						
Number of carriers	34	68	43	76	27	26
Mean ± SD follow-up (yrs)*	20 ± 8	18 ± 8	19 ± 8	15 ± 9	17 ± 9	17 ± 8

*Follow-up age counted until time to beta-blocker treatment, or age 16 (for younger age group analyzed). By definition, subjects age 16–40 years had to survive until age 16 without cardiac events and without beta-blocker treatment.
LQTS = long QT syndrome. Other abbreviations as in Abbreviations box.

Table 2. Clinical Characteristics of LQTS Carriers by Genotype and Gender

	LQT1		LQT2		LQT3	
	Males (n = 108)	Females (n = 135)	Males (n = 88)	Females (n = 121)	Males (n = 42)	Females (n = 39)
ECG parameters†						
Age ≤15 yrs	n = 34	n = 31	n = 22	n = 16	n = 16	n = 12
Age at ECG (yrs)	6 ± 4	7 ± 5	6 ± 6	8 ± 6	6 ± 5	5 ± 5
RR (ms)	717 ± 177	730 ± 206	638 ± 185	649 ± 137	804 ± 304	613 ± 179
QTc (ms)	490 ± 45	487 ± 35	477 ± 30	475 ± 56	528 ± 45	469 ± 43*
Age 16–40 yrs	n = 14	n = 27	n = 20	n = 32	n = 14	n = 15
Age at ECG (yrs)	28 ± 9	29 ± 8	30 ± 8	27 ± 8	26 ± 8	26 ± 8
RR (ms)	921 ± 209	909 ± 169	932 ± 187	878 ± 127	1,146 ± 291	852 ± 148*
QTc (ms)	469 ± 22	473 ± 31	466 ± 34	490 ± 45*	515 ± 48	499 ± 32
Cardiac events						
Carriers with ≥1 cardiac event	55 (51%)	72 (53%)	30 (34%)	62 (51%)*	7 (17%)	7 (18%)
Median age at 1st cardiac event	8	12	11	16	16	19
Recurrent cardiac events‡	30 (57%)	46 (67%)	14 (54%)	41 (71%)	0	2 (33%)
Median cardiac event rate‡	0.15	0.14	0.08	0.12	0.03	0.09*
Aborted cardiac arrest or LQTS death	5 (5%)	10 (7%)	1 (1%)	11 (9%)*	1 (3%)	1 (3%)

*$p < 0.05$ when comparing males versus females of the same LQTS type; †ECG parameters are reported for first ECGs recorded off beta-blockers during specific age groups in family members while excluding probands; numbers of carriers with ECGs recorded ≤15 years and at age 16–40 years are provided (subjects with first ECG recorded after age 40 are not included), patients without ECGs recorded off beta-blockers during respective age periods are not included in the analysis. Welsh *t* tests were used for testing; ‡Recurrent cardiac events and cardiac event rates per patient per year were calculated only in patients who survived first cardiac event: 53 LQT1 males, 69 LQT1 females, 26 LQT2 males, 58 LQT2 females, 7 LQT3 males, and 6 LQT3 females, individual cardiac event rates were capped at the level of five cardiac events per patient per year. Wilcoxon rank-sum tests were used for continuous variables and chi-square tests for binary variables.

ECG = electrocardiographic; LQTS = long QT syndrome. Other abbreviations as in Abbreviations box.

specific subgroups. Lethality of cardiac events, defined as the number of deaths divided by the total number of cardiac events (6), was compared between males and females by gender in genotype groups. These analyses were performed for cardiac events occurring before beta-blocker treatment.

Statistical analysis. To compare characteristics of males and females within genotype, Welsh *t* tests and Wilcoxon rank-sum tests were used for continuous variables, and chi-square tests were used for binary variables. The distributions of time to first cardiac event, stratified by genotype, gender, and age were estimated using the Kaplan-Meier method. For the analysis of children, birth was used as the time origin, whereas for event-free adults, age 16 was considered as the time origin. Stratified Cox proportional hazards models, allowing for separate baseline hazard functions for each genotype, were used to model the conditional relationships of gender with time to first cardiac event within each genotype and age group, adjusted for QTc at first ECG (regardless of age at ECG). In order to make the assumptions of proportional hazards plausible, separate Cox models were fit for children, ignoring follow-up beyond age 16, and adults who survived to age 16 without events (or beta-blocker therapy). Grouped jackknife estimates of standard errors were used to adjust p values and confidence intervals for within-family dependence not directly modeled by the stratified Cox models (15).

RESULTS

ECG characteristics of LQTS carriers. Table 2 shows off-beta-blocker RR and QTc values from ECGs recorded during specific age periods (well matched for age among males and females) for LQTS carriers while excluding probands. In childhood, LQT3 males had a higher QTc duration and lower heart rate than LQT3 females, whereas there was no gender difference in QTc duration and heart rate among LQT1 and LQT2 carriers. In LQT1 adults, there was no gender difference in QTc and heart rate, whereas LQT2 females had significantly longer QTc and somewhat faster heart rate than LQT2 males; LQT3 adult males had a longer QTc and slower heart rate than adult LQT3 females.

When comparing by age within gender-genotype subgroups, the QTc duration was longer in LQT1 children than in LQT1 adults regardless of gender. There was no such age-related difference in LQT2 males, whereas LQT2 and LQT3 females had QTc longer in adulthood than in childhood.

Cardiac events in LQTS carriers age ≤15 years. There were 165 patients with first cardiac event before beta-blocker treatment among 533 LQTS carriers age ≤15 years. Figure 1 shows the cumulative probability of a first cardiac event in female versus male LQTS carriers age ≤15 years by genotype, and the left panel of Table 3 shows hazard ratios (HR) for females versus males, adjusted for QTc duration, in the same groups. There was a significantly lower risk of cardiac events in LQT1 females than in LQT1 males (HR = 0.58; p = 0.005). In LQT2 and LQT3 children, there was no significant difference between male and female carriers. When comparing by genotype, the cumulative probability of a first cardiac event by age 15 years was 56% in LQT1 males, 42% in LQT1 females, 33% in LQT2 males, 27% in LQT2 females, and 6% to 8% in LQT3 males

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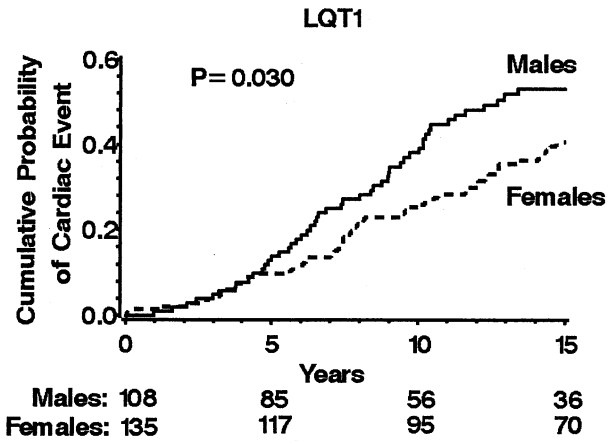
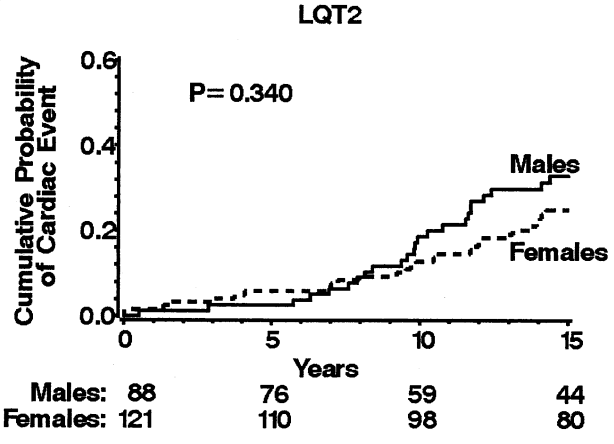




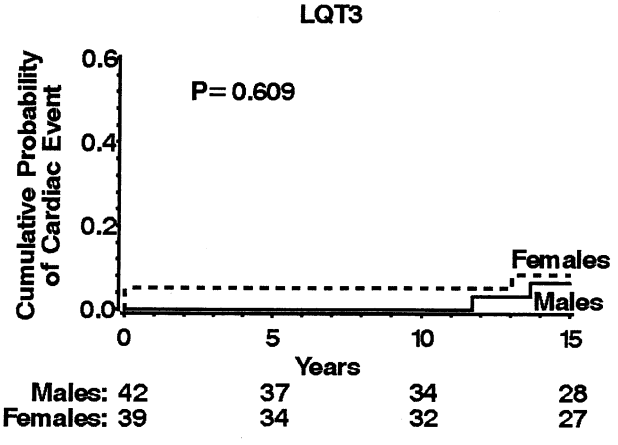
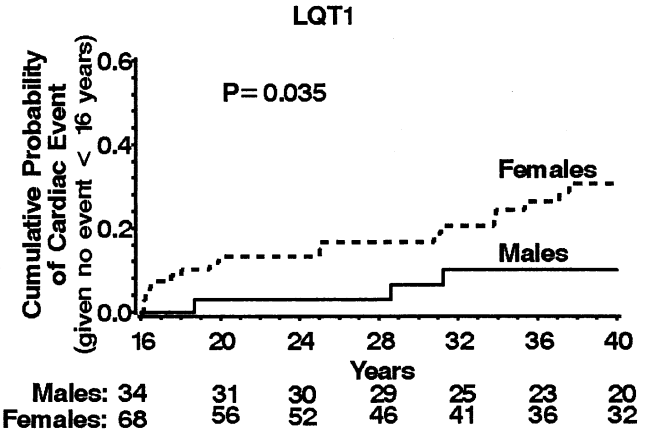
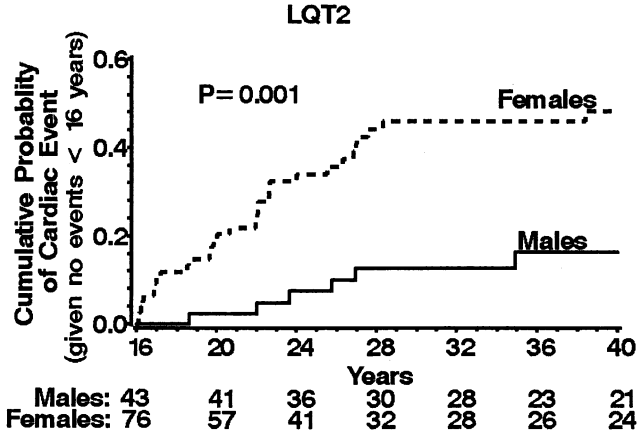


Figure 1. Cumulative probability of the first cardiac event in long QT syndrome carriers age ≤ 15 years by gender and genotype. P value is computed based on multivariate Cox model. Observation time censored at age 16 years. Numbers of males and females at risk are provided. See Abbreviations box for definitions.





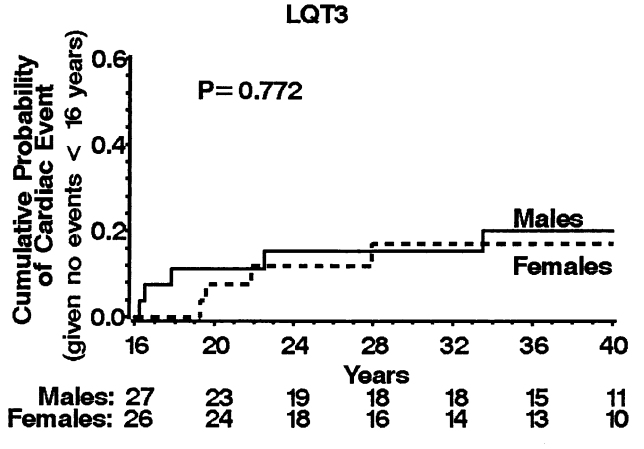


Figure 2. Cumulative probability of the first cardiac event in long QT syndrome carriers age 16 to 40 years by gender and genotype, conditional on no cardiac event before age 16. P value is computed based on multivariate Cox model. Observation time is 16 to 40 years. Numbers of males and females at risk are provided. See Abbreviations box for definitions.

Table 3. Relative Hazards of First Cardiac Event by LQTS Genotype and Age

	533 LQTS Carriers Age 0–15 Years		274 LQTS Carriers Age 16–40 Years Without Prior Events	
	HR (95% CI)†	p Value†	HR (95% CI)†	p Value†
Females vs. Males				
LQT1	0.58 (0.40, 0.84)	0.005	3.35 (1.40, 8.02)	0.007
LQT2	0.73 (0.43, 1.25)	0.252	3.71 (1.37, 10.07)	0.010
LQT3	1.84 (0.47, 7.25)	0.384	0.90 (0.29, 2.82)	0.854
QTc*	1.07 (1.04, 1.11)	< 0.001	1.08 (1.08, 1.12)	< 0.001

Models based on stratified (by LQT type) Cox proportional hazards models, adjusted for QTc, with 165 first cardiac events in 533 persons through age 15 and 68 first cardiac events in 274 persons without cardiac events before age 16. *HR for a 10 ms increase in QTc value; †Confidence intervals and p values have been adjusted for the weak within-family dependence via grouped jackknife robust variance estimation (15).

CI = confidence interval; HR = hazards ratio; LQTS = long QT syndrome. Other abbreviations as in Abbreviations box.

or females (Fig. 1). The results of the analyses were very similar when using first cardiac event regardless of beta-blocker use (not shown).

Cardiac events in LQTS carriers age 16 to 40 years. There were 68 patients with first cardiac event before beta-blocker treatment among 274 LQTS carriers who survived to age 16 without any cardiac events. Figure 2 shows the cumulative probability of a first cardiac event, conditional on survival to age 16 without event, in female versus male LQTS carriers age 16 to 40 years by genotype. The right panel of Table 3 shows HRs for females versus males, adjusted for QTc duration in the same groups. Compared with males, females had a significantly higher risk of first cardiac event among both LQT1 and LQT2 carriers, but not LQT3 carriers. When comparing by genotype (and confined to patients without events before age 16), the cumulative probability of first cardiac event between age 16 and 40 years was 48% in LQT2 females, 31% in LQT1 females, and 10% to 20% in LQT1 males, LQT2 males, and LQT3 males and females (Fig. 2). The results of the analyses were very similar when using first cardiac event regardless of beta-blocker use (not shown).

Recurrent cardiac events in LQTS carriers. The analysis of recurrent cardiac events and severity of clinical course was conducted in LQTS carriers who had survived their first cardiac event (Table 2): 122 (51%) LQT1 carriers, 84 (42%) LQT2 carriers, and 13 (16%) LQT3 carriers. There were no significant differences in the risk of recurrent cardiac events before beta-blocker treatment between males and females in all three genetic LQTS types. Cardiac event rates per patient per year were not significantly different between males and females in LQT1 and LQT2 carriers and were higher in LQT3 females than males. This analysis was not performed separately in age groups ≤ and >15 years because the numbers of symptomatic patients per age-subgroup were limited.

Sudden death and lethality of cardiac events in family members from genotyped LQTS families. Table 4 shows cardiac events and sudden death (presumably LQTS death) in all directly related family members from families with known genotype, regardless of ECG recording or genetic testing, therefore including both affected and unaffected family members from the side of a family with LQTS genetically confirmed. The occurrence of at least one cardiac event and recurrent cardiac events were higher in male and female LQT1 family members and in female LQT2 family members than in male LQT2 family members and male and female LQT3 family members. The total number of cardiac events was much higher in female LQT1 and LQT2 family members than in all other groups, indicating a higher risk of recurrent cardiac events in these two subsets.

There were 84 sudden deaths before age 40 years in directly related family members. In childhood, the occurrence of death was somewhat higher in male than female LQT1 family members, whereas it was similarly low in males and females from LQT2 and LQT3 families. In

Table 4. Cardiac Events and Sudden Death in LQTS Family Members by Family Genotype and Gender

	LQT1		LQT2		LQT3	
	Males (n = 516)	Females (n = 559)	Males (n = 453)	Females (n = 523)	Males (n = 173)	Females (n = 151)
Median follow-up time (yrs)	24	27	25	27	25	20
Cardiac events						
Family members with ≥1	104 (20%)	125 (22%)	67 (15%)	134 (26%)*	22 (13%)	20 (13%)
Family members with ≥2	53 (10%)	70 (13%)	29 (7%)	75 (15%)*	6 (4%)	8 (5%)
Total number of cardiac events	403	897	172	1062	37	40
Death						
At age 0–15 yrs	16 (3%)	6 (1%)*	2 (<1%)	1 (<1%)	3 (2%)	1 (1%)
At age 16–40 yrs	3 (1%)	13 (3%)	8 (2%)	21 (5%)	4 (3%)	6 (4%)

*p < 0.05 when comparing males versus females of the same LQTS type using chi-square test.

LQTS = long QT syndrome. Other abbreviations as in Abbreviations box.

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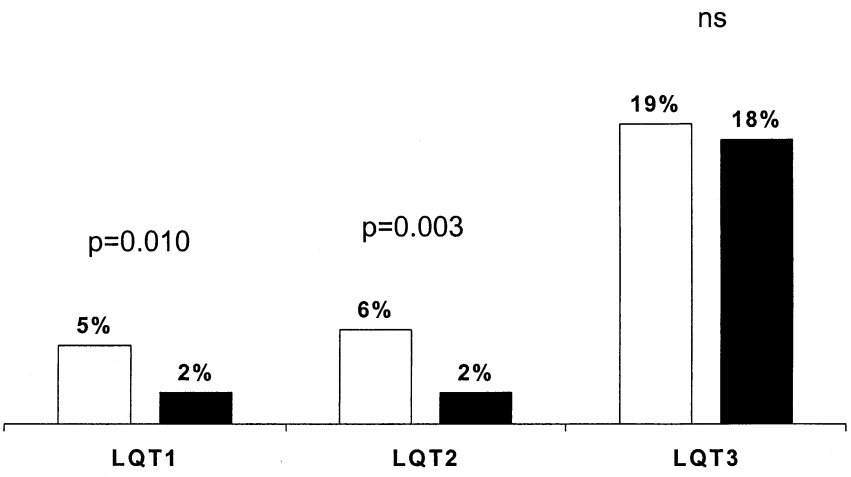

Figure 3. The lethality of cardiac events analyzed by sex in long QT syndrome (LQTS) family members with known genotype. **Open bars** = males; **black bars** = females. $p < 0.001$ when comparing LQT3 males and females to LQT1 and LQT2 males and females, respectively. For abbreviations see Abbreviations box.

adulthood, the occurrence of death was higher in female than male LQT2 family members. However, the lethality of cardiac events was higher in males than females from either LQT1 or LQT2 families (Fig. 3). The lethality of cardiac events in male and female LQT3 family members was similar, but was significantly higher than in LQT1 and LQT2 families.

DISCUSSION

In this study, we found that the LQTS genotype influences the probability of cardiac events differently in male and female children and adult LQTS patients, indicating a genotype-specific modulating effect of age and gender primarily in LQT1 and LQT2, but not in LQT3 patients.

During childhood, the risk of cardiac events was significantly higher in LQT1 males than in LQT1 females. In LQT2 and LQT3 children, there was no significant difference between males and females in the risk of cardiac events. When comparing the risk of cardiac events by genotype and gender during childhood, LQT1 males were the group at highest risk with a 56% cumulative probability of a cardiac event by age 15 years, independently of QTc duration; LQT1 females had a 40% risk, whereas LQT2 males and females had a 30% risk of experiencing cardiac events by age 15 years; LQT3 children had a low risk of cardiac events.

Among adults who remained event-free until age 16, LQT2 and LQT1 females had a significantly increased risk of cardiac events compared with males of the same genotype, again, independently of QTc duration; LQT1 and LQT2 males and LQT3 females and males, who survived until age 16 without events, had a lower risk of cardiac events, unless they presented with a substantial QTc prolongation. This analysis demonstrates that the hazard of cardiac events diminishes substantially with age in LQT1 and LQT2 males, and also decreases somewhat in LQT1 females. In LQT2 females, there is an increased risk of cardiac events both during childhood and adulthood. Although the overall number of cardiac events in LQT3 patients was small, there was no trend toward age- and gender-dependency of the risk in these patients. The above findings indicate that vulnerability to cardiac events changes primarily with age in LQTS males with potassium channel gene abnormalities. The risk of cardiac events in LQTS females with potassium channel genes mutations remains increased both during childhood and adulthood. Importantly, the above analyses showed similar results when using first cardiac event regardless of beta-blocker use.

Recurrent cardiac events are most prevalent in LQT1 and LQT2 females with simultaneous low lethality of cardiac events in these two groups indicating a high likelihood of self-terminating episodes of torsades de pointes. The lethality of cardiac events is the highest in LQT3 males and females (19% and 18%, respectively), and higher in LQT1 males than females (5% vs. 2%, respectively) and in LQT2 males than females (6% vs. 2%, respectively).

The effectiveness of beta-blocker therapy in LQTS patients was the subject of our prior study (14) in which we demonstrated that in about 70% of patients beta-blockers are effective in preventing subsequent cardiac events whereas cardiac events continue to occur in the remaining 30% despite beta-blocker treatment. In that paper we also analyzed the effectiveness of beta-blockers by genotype and found that beta-blockers are associated with a significant reduction in cardiac event occurrence and rates in LQT1 and LQT2 patients. There was, however, a trend for a better effectiveness of beta-blockers in LQT1 than in LQT2 patients. We did not perform an analysis of the effectiveness of beta-blockers by age, gender, and genotype in this paper because we have limited statistical power to carry out such an analysis in so many subgroups.

The overall age-related decrease in the risk of cardiac events in LQT1 and LQT2 males does not have a clear explanation. It is likely that increased levels of androgens and decreased heart rate after puberty contribute to this

phenomenon (16). Because there is no evidence for gender-related differences in the risk of cardiac events in LQT3 adults, it is likely that male (and/or female) hormones modulate function of potassium, but not sodium channels.

Simultaneously, the concept of decreased density of potassium currents in the myocardium of females, as observed in animal models (17), seems to provide a plausible explanation for gender-related differences in propensity to cardiac events among patients carrying IKr or IKs channel gene mutations. Higher lethality of cardiac events in LQT3 males and females could be attributed to increased transmural heterogeneity of repolarization observed in pharmacological models of sodium channel dysfunction (18). It is possible that a higher lethality of cardiac events in LQT1 and LQT2 males than LQT1 and LQT2 females is related to a generally slower heart rate in adult males, eventually precipitating more non–self-terminating torsades de pointes.

These gender- and age-related differences in clinical course of the disease are accompanied by sex- and age-related differences in QTc duration and heart rate. Although previous studies showed significantly longer QTc duration in adult LQTS females than males (7–11), we could confirm these previous findings only in LQT2 carriers, but not in LQT1 and LQT3 carriers. In fact, LQT1 children showed longer QTc duration than LQT1 adults regardless of gender.

Long QT syndrome patients who were event free until age 16 years may represent a more benign course of the disease in adulthood. However, our data demonstrate that the clinical course is not homogenous in various genetic types of LQTS stratified by age and gender. The 48% cumulative probability of cardiac events in LQT2 females between age 16 and 40 years is higher or comparable to the cumulative probability of cardiac events in most LQTS children except LQT1 males who show a higher (56%) risk. We believe that this observation is of major importance and emphasizes a need to carefully follow and treat adult LQTS patients (particularly females) who remain at high risk of cardiac events despite asymptomatic course in childhood and adolescence. The differences in the clinical course of LQTS are most likely determined by genetic background of the disorder and by different penetrance of the disease even inside the same family carrying the same mutation, as demonstrated by Priori et al. (19). Some additional causative conditions (e.g., varying degree of repolarization heterogeneity in the myocardium) and modulating factors (e.g., varying susceptibility to sympathetic activation) might operate in LQTS carriers who, despite ion channel gene mutation and prolonged QTc, do not develop cardiac events.

Our findings that the risk of cardiac events and lethality of cardiac events vary depending on age and gender in different genetic types of LQTS, and observations on age- and gender-related differences in QTc duration, indicate differential modulating effects of age and gender on the clinical manifestation of LQTS.

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REFERENCES

1. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.
2. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long QT syndrome. N Engl J Med 1992;327:846–52.
3. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. Circulation 1993;88:782–84.
4. Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol 1999;10:1664–83.
5. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes: KCNQ1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102:1178–85.
6. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long QT syndrome. N Engl J Med 1998;339:960–5.
7. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
8. Zareba W, Moss AJ, le Cessie S, et al. Risk of cardiac events in long QT syndrome family members. J Am Coll Cardiol 1995;26:1685–91.
9. Locati EH, Zareba W, Moss AJ, et al. Age and sex-related differences in cardiac events in patients with congenital long QT syndrome: findings from the International LQTS registry. Circulation 1998;97:2237–44.
10. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–5.
11. Lehmann MH, Timothy KW, Frankovich D, et al. Age-sex influence on the rate-corrected QT interval and the QT-heart rate relation in families with genotypically characterized long QT syndrome. J Am Coll Cardiol 1997;29:93–9.
12. Moss AJ, Zareba W, Benhorin J, et al. Electrocardiographic T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995;92:2929–34.
13. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave pattern and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000;102:2849–55.
14. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long QT syndrome. Circulation 2000;101:616–23.
15. Thernau T, Granbsch PM. Modeling Survival Data: Extending Cox Model. New York, NY: Springer, 2000.
16. Bidoggia H, Maciel JP, Capalozza N, et al. Sex differences on the electrocardiographic pattern of cardiac repolarization: possible role of testosterone. Am Heart J 2000;40:678–83.
17. Liu XK, Katchman A, Drici MD, et al. Sex difference in the cycle length-dependent QT and potassium currents in rabbits. J Pharmacol Exp Ther 1998;285:672–9.
18. Shimizu W, Antzelevitch C. Cellular basis for long QT, transmural dispersion of repolarization, and torsade de pointes in the long QT syndrome. J Electrocardiol 1999;32 Suppl:177–84.
19. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long QT syndrome: clinical impact. Circulation 1999;99:529–33.