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Age-Gender Influence on the Rate-Corrected QT Interval and the QT-Heart Rate Relation in Families With Genotypically Characterized Long QT Syndrome

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Objectives. **We sought to analyze age-gender differences in the rate-corrected QT (QTc) interval in the presence of a QT-prolonging gene.**

Background. **Compared with men, women exhibit a longer QTc interval and an increased propensity toward torsade de pointes. In normal subjects, the QTc gender difference reflects QTc interval shortening in men during adolescence.**

Methods. **QTc intervals were analyzed according to age (<16 or ≥16 years) and gender in 460 genotyped blood relatives from families with long QT syndrome linked to chromosome 11p (KVLQT1; n = 199), 7q (HERG; n = 208) or 3p (SCN5A; n = 53).**

Results. **The mean QTc interval in genotype-negative blood relatives (n = 240) was shortest in men, but similar among women, boys and girls. For genotype-positive blood relatives, men exhibited the shortest mean QTc interval in chromosome 7q- and 11p-linked blood relatives (n = 194), but not in the smaller 3p-linked group (n = 26). Among pooled 7q- and 11p-linked blood relatives, multiple regression analysis identified both genotype ($p < 0.001$) and age-gender group (men vs. women/children; $p < 0.001$) as significant predictors of the QTc interval; and heart rate ($p < 0.001$), genotype ($p < 0.001$) and age-gender group ($p = 0.01$) as significant predictors of the absolute QT interval. A shorter mean QT interval in men was most evident for heart rates <60 beats/min.**

Conclusions. **In familial long QT syndrome linked to either chromosome 7q or 11p, men exhibit shorter mean QTc values than both women and children, for both genotype-positive and -negative blood relatives. Thus, adult gender differences in propensity toward torsade de pointes may reflect the relatively greater presence in men of a factor that blunts QT prolongation responses, especially at slow heart rates.**

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It is now appreciated that women are more susceptible to the development of torsade de pointes in various settings of QT prolongation (1–7). It remains unclear whether such relative gender differences in adults reflect an intrinsically greater tendency in women to develop torsade de pointes or whether men have some protective factor(s).

Investigations of physiologic age-gender differences in the rate-corrected QT interval (QTc) offer indirect insights into this problem. Although it has long been recognized that cardiac repolarization at comparable heart rates or after correction for different heart rates is of longer duration in women compared with men (8–11), neonates (12) and older children (13,14) do not exhibit such gender differences in the QTc interval. Extensive electrocardiographic (ECG) data reported by Rautaharju et al. (15) indicate that the gender-related divergence in the QTc interval ("QT index") after childhood actually reflects shortening of this interval in men (during adolescence) rather than prolongation in women. It would be important to determine, therefore, whether a similar age-gender relation can be observed in the presence of a QT-prolonging influence.

Families with inherited cardiac ion-channel mutations that prolong repolarization (16–18) provide a useful clinical model for investigating this question. Indeed, Hashiba (19) observed that in families with autosomal dominant long QT syndrome, women tend to have longer QTc intervals than men, and that such differences appear to result from postpubertal QTc shortening in men. These observations, however, were limited to a phenotypic analysis that did not allow for determination of QTc intervals separately in genotype-positive and -negative blood relatives. To gain further insight into how the QTc disparity between women and men arises developmentally in

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
QTc = rate-corrected QT interval

families with long QT syndrome, we undertook a study of age-gender differences in duration of cardiac repolarization utilizing families in whom genetic linkage and mutational studies enabled us to distinguish long QT gene carriers from noncarriers.

Methods

Twenty-two multigenerational families with hereditary, autosomal dominant (Romano-Ward) long QT syndrome, living in North America, formed the basis of this study. All the families were genotypically characterized. In three families (total of 199 blood relatives), described in previous reports (18,20,21), long QT syndrome was shown to be linked to chromosome 11p (LQT1) at a locus encoding for a probable novel potassium channel gene, KVLQT1 (18). In another 15 families (total of 208 blood relatives), described in other recent studies (16,22,23), the long QT trait was shown to be linked to chromosome 7q (LQT2) at the human ether-á-go-go–related potassium channel gene (HERG) locus (16). In the remaining four families (total of 53 blood relatives), long QT syndrome was linked to the sodium channel gene SCN5A locus on chromosome 3p (LQT3) (17). Participating family members gave their written informed consent to be part of ongoing ECG-genetic studies approved by human investigation committees at the participating institutions.

For consistency, RR and QT intervals, corrected for rate using the Bazett formula (8), were measured in one laboratory (LDS Hospital), as previously described (24). Electrocardiograms were recorded with various machines at a paper speed of 25 mm/s, and QT and RR intervals were measured in lead II (or lead V_5 if lead II was technically unsatisfactory). Genetic linkage and mutational analyses (16–18) permitted blood relatives and their QTc intervals to be classified as genotype-positive or -negative, according to the presence or absence of a DNA marker completely linked to the long QT gene within a given family. Electrocardiograms were read without knowledge of genotype status. None of the blood relatives had intraventricular conduction disturbances and none were taking QT-prolonging medication at the time of the index ECG.

Statistical analysis. An age cutoff of ≥16 years was used to differentiate adults from children, as in a previous ECG analysis defining ranges of normal QTc (25) intervals. Although QTc data are presented for each of the three genotypic variants, more detailed ECG and statistical analyses were confined to pooled data from chromosome 11p- and 7q-linked families, for reasons described in the Results section. Variability of QTc interval within each age-gender-genotype group was measured by coefficient of variation. The effect on QTc interval of age (dichotomized at 16 years), genotype, gender and heart rate was performed using analysis of variance and multiple regression analysis, including assessment of possible two-factor interactions. Comparison of mean QTc and QT values between groups (e.g., men vs. women) was made using least squares means analysis. Categoric variables were compared using the chi-square test. No adjustment was made for multiple comparisons (26), and all hypothesis tests were two-tailed. Statistical significance was defined by $p < 0.05$.

Table 1. Demographic Characteristics and Genotype Distribution in Long QT Syndrome Blood Relatives by Chromosomal Linkage

	3p (n = 53)	7q (n = 208)	11p (n = 199)
Male gender	66%*	43%	45%
Age <16 yr	38%	33%	51%†
Genotype positive	49%	53%‡	42%

*$p < 0.01$ versus chromosome 7q- or 11p-linked blood relatives. †$p < 0.001$ versus chromosome 7q-linked blood relatives. ‡$p < 0.02$ versus chromosome 11p-linked blood relatives.

Results

Demographic characteristics of the study group, by chromosomal linkage, are provided in Table 1. The proportion of males was greatest in chromosome 3p-linked families, and children had the largest representation in the chromosome 11p-linked families. Overall, 220 (49%) of the 460 blood relatives were genotype positive, the highest prevalence being observed in chromosome 7q-linked families. Only 21 (10%) of genotype-positive blood relatives studied with relevant information (n = 219) were taking beta-blockers (0%, 15% and 5%, respectively, for chromosome 3p, 7q and 11p) at the time of the index ECG.

Patterns of age-gender differences in QTc interval for each of the three long QT family genotypes. Figures 1 and 2 show mean QTc interval values for genotype-negative and -positive blood relatives, respectively, from chromosome 11p-, 7q-, and 3p-linked families, according to age and gender. As expected, for each of the four age-gender groups, the mean QTc interval was significantly longer in genotype-positive blood relatives than in their genotype-negative counterparts ($p < 0.0001$), regardless of chromosome linkage group. For genotype-negative blood relatives (Fig. 1), the mean QTc interval of women was similar to that of male and female children; only in men did the mean QTc interval appear to differ—being shorter compared with both women and children, for all three linkage types.

For genotype-positive blood relatives (Fig. 2) we observed greater variation in the mean QTc interval among age-gender groups, compared with their genotype-negative counterparts. Both chromosome 11p- and 7q-linked genotype-positive blood relatives, however, exhibited the familiar finding of a longer mean QTc interval in women than in men. In contrast, among the chromosome 3p genotype-positive blood relatives, men

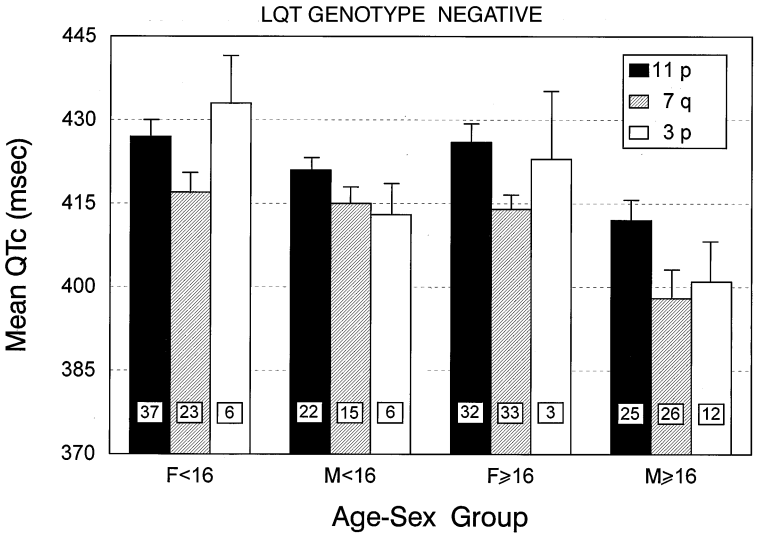

Figure 1. Mean QTc interval by age-gender group in genotype-negative blood relatives from 11p-linked (**solid bars**), 7q-linked (**hatched bars**) and 3p-linked (**open bars**) families with long QT (LQT) syndrome. Number of blood relatives for each chromosome subset within each age-gender group is shown near bottom of bars; SEM indicated above bars. An age cutoff of 16 years was used to demarcate adulthood. F = female; M = male.

had a longer mean QTc interval compared with women. Because of the rather small sample sizes (range 3 to 12) and male-skewed nature of the chromosome 3p genotype-positive (as well as negative) age-gender groups, and the fact that QTc differences between *adult* females and males were at variance with the normative difference we were attempting to better understand through this study (i.e., shorter mean values in men, even for long QT syndrome families [19]), chromosome 3p-linked blood relatives—both genotype negative and positive—were excluded from further analysis. Accordingly, the remaining data that are presented apply exclusively to pooled results of chromosome 7q- and 11p-linked families.

Age-gender differences in QTc interval for chromosome 7q- and 11p-linked families. Mean QTc values by age, gender and genotype in the pooled cohort of blood relatives from chromosome 7q- and 11p-linked families are provided in Table 2. Within each age-gender group, the coefficient of variation for the QTc interval was greater for genotype-positive (range 5.8 to 9.2) than for genotype negative (range 3.8 to 5.7) individuals. Despite these differences in QTc variability related to genotype status, men consistently exhibited mean QTc values 12 to 22 ms shorter than those of either women or children (i.e., both among blood relatives who were genotype negative [$p = 0.001$ to 0.004] and among those who were genotype positive [$p = 0.02$ vs. women and girls, and $p = 0.13$ vs. boys]). In contrast, women had mean QTc values similar to (within ± 1 ms of) the mean values in female and male children of corresponding genotype ($p = 0.56$ vs. mean QTc of 421 ± 18 ms for *pooled* female and male genotype-negative children, and $p = 0.84$ vs. mean QTc of 489 ± 30 ms in *pooled* female and male genotype-positive children). It should be mentioned that when adulthood was defined by an age cutoff of 12 years instead of 16 years, age-gender differences in mean QTc interval qualitatively identical to those in Table 2 were still observed, for both genotype-negative and -positive blood relatives.

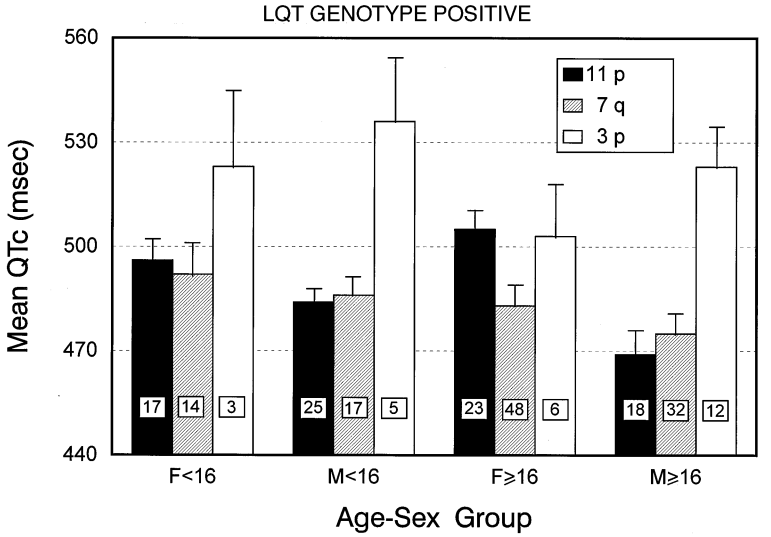

Figure 2. Mean QTc interval by age-gender group in genotype-positive blood relatives from 11p-linked (**solid bars**), 7q-linked (**hatched bars**) and 3p-linked (**open bars**) families with long QT (LQT) syndrome. Format and abbreviations as in Figure 1.

Table 2. Mean Rate-Corrected QT Values in Blood Relatives From Pooled Genotypically Characterized Long QT Syndrome Families Linked to Chromosome 7q (HERG) or 11p (KVLQT1)

	Age 0–15 yr		Age >16 yr		p Values*		
	Female (A)	Male (B)	Female (C)	Male (D)	D vs. A	D vs. B	D vs. C
Genotype negative	423 ± 19 (n = 60)	418 ± 16 (n = 37)	420 ± 23 (n = 65)	405 ± 23 (n = 51)	0.001	0.004	0.001
Genotype positive	494 ± 33 (n = 31)	485 ± 28 (n = 42)	490 ± 45 (n = 71)	473 ± 33 (n = 50)	0.02	0.13	0.02

*p values determined using analysis of variance and least squares means. Data shown as mean rate-corrected QT intervals ± SD in $ms^{1/2}$.

Relation of QTc interval to age-gender differences in heart rate. Given that the QTc interval is inversely related to the square root of heart rate in the Bazett formula, the QTc interval might shorten simply as a result of an increase in the RR interval, without necessitating any change in absolute QT value. We therefore investigated whether the gender-dependent QTc differences that arise in adulthood might be attributable to selective heart rate slowing in men.

Mean heart rates for the pooled chromosome 7q- and 11p-linked families, broken down by age, gender and genotype, are provided in Table 3. Mean heart rate was slightly but insignificantly faster in young female blood relatives compared with their male counterparts, both among those who were genotype negative (6 beats/min difference, $p = 0.21$) and genotype positive (5 beats/min difference, $p = 0.25$). Although similar differences between males and females were observed in adults, for either genotype, mean heart rate was lower for adults of *both* genders compared with their younger counterparts. The magnitude of this change in rate was similar in males and females, for both genotypically negative (27 beats/min decrease in both genders) and genotypically positive (22 and 25 beats/min decreases, respectively) blood relatives.

It should be noted that mean absolute QT intervals were longer in adults than in children for both genotype categories (Table 4). These results further indicate that a rate artifact alone cannot account for the observed age-gender differences in the QTc interval.

Variables predictive of QTc interval in men versus women and children. The potential influences of genotype, age-gender group (men vs. women and children combined) and heart rate on the QTc interval in pooled blood relatives from chromosome 7q- and 11p-linked families were assessed by multiple regression analysis. As shown in Table 5, both genotype and age-gender group were shown to be statistically significant predictors of the QTc interval. A small but statistically significant interaction between age-gender group and heart rate (which was also a statistically significant predictor) was identified. In view of this possible confounding effect, presumably reflecting imperfect correction for rate by the Bazett formula (27), we also analyzed the QT-heart rate relation by age-gender group and genotype.

Comparison of QT-heart rate relation in men versus women and children. Mean absolute QT values for the pooled chromosome 7q- and 11p-linked blood relatives were calculated for each of three ranges of heart rate: <60 beats/min, 61 to 80 beats/min and 81 to 100 beats/min (higher heart rates were not analyzed owing to fewer than three men with rest rates >100 beats/min, for either genotype). Plots of the mean QT intervals for the three heart rate ranges are shown in Figures 3 and 4 (for genotype-negative and -positive blood relatives, respectively). Note that within each range of heart rate, mean values of that variable for men versus women and children combined were within 1 to 2 beats/min of one another.

As expected, the mean QT intervals varied inversely with heart rate, for both genotypes and age-gender groups. At heart rates <60 beats/min, however, men had shorter mean QT values than women and children (mean difference of 20 ms for genotype-negative [$p < 0.04$] and 24 ms for genotype-positive blood relatives [$p = 0.052$]).

Multiple regression analysis was performed to assess the influence of heart rate as a continuous variable, genotype and age-gender group (men vs. women and children) on the QT interval (Table 6). Although heart rate and genotype were found to be the most powerful predictors, age-gender group

Table 3. Mean Heart Rates in Blood Relatives From Pooled Genotypically Characterized Long QT Syndrome Families Linked to Chromosome 7q (HERG) or 11p (KVLQT1)

	Age 0–15 yr		Age ≥16 yr	
	Female	Male	Female	Male
Genotype negative	97 ± 24 (n = 60)	91 ± 22 (n = 37)	70 ± 11* (n = 65)	64 ± 11* (n = 51)
Genotype positive	92 ± 18 (n = 31)	87 ± 22 (n = 42)	67 ± 15* (n = 71)	65 ± 14* (n = 50)

*$p < 0.001$ versus young blood relatives of same gender and genotype. Data shown as mean heart rate ± SD in beats/min.

Table 4. Mean Absolute QT Values in Blood Relatives From Pooled Genotypically Characterized Long QT Syndrome Families Linked to Chromosome 7q (HERG) or 11p (KVLQT1)

	Age 0–15 yr		Age ≥16 yr	
	Female	Male	Female	Male
Genotype negative	340 ± 44 (n = 60)	346 ± 37 (n = 37)	391 ± 34* (n = 65)	395 ± 31* (n = 51)
Genotype positive	405 ± 53 (n = 31)	413 ± 61 (n = 42)	469 ± 61* (n = 71)	461 ± 50* (n = 50)

*$p < 0.0001$ versus young blood relatives of same gender and genotype. Data shown as mean QT interval QT ± SD in ms.

Table 5. Multiple Regression Analysis of Variables Predictive of Rate-Corrected QT Interval in Pooled Genotypically Characterized Long QT Syndrome Families Linked to Chromosome 7q (HERG) or 11p (KVLQT1)

Variable	Contribution to Model R^2*	Regression Coefficient (beta)	SE (beta)	p Value
Genotype (+/−)	0.560	0.0685	0.0029	<0.001
Age-gender group (adult men/others)	0.023	0.0600	0.0167	<0.001
Heart rate–age-gender interaction	0.008	−0.0007	0.0002	<0.01
Heart rate	0.004	0.0015	0.0005	<0.01

*Model R^2 = 0.595.

also had a modest, statistically significant influence on the QT interval. A small, statistically significant heart rate–genotype interaction was also observed (reflecting somewhat slower rates in genotype-positive blood relatives [Table 3], possibly related to beta-blocker use in a subset of these cases), but this does not confound the significance of age-gender group as a predictor of QT interval.

Discussion

The present study provides new information on developmental changes that give rise to gender differences in the duration of cardiac repolarization seen in adults, in the presence of a QT-prolonging gene. At least for chromosome 7q (HERG)- and 11p (KVLQT1)-linked families, which harbor cardiac potassium channel mutations and account for the majority of cases of hereditary long QT syndrome genotyped thus far (16–18), we observed that, in both long QT gene carriers and noncarriers, male and female children manifested similar QTc intervals; among adults, however, a QTc abbreviation was seen in men without any corresponding change from childhood in women.

Although genotype-negative blood relatives from chromosome 3p-linked families exhibited a similar pattern, no clear age-gender differences were evident among their genotype-positive counterparts. Whether this discordance simply reflects the small sample size studied or, instead, truly unique behavior of families with SCN5A mutations (as has been described with regard to T wave patterns [28] and pharmacologic responses [29]), remains to be determined.

Comparison with previous studies. Our findings in children from chromosome 7q- and 11p-linked long QT syndrome families are consistent with a recent report documenting a similarity in QTc intervals in normal male and female neonates (12) and earlier studies in older prepubertal boys and girls (13,14). In a previous, very large ECG demographic study in normal subjects, Rautaharju et al. (15) documented persistence of the juvenile rate-corrected (non-Bazett) QT interval in women, in contrast to a postpubertal shortening of repolarization time in men. Our observations not only confirm these findings in normals, but go further by demonstrating that this same developmental gender dichotomy also gives rise to the relatively greater magnitude of QTc prolongation in women versus men harboring a chromosome 7q- or 11p-linked long QT gene. These findings are consistent with the phenotypic analysis of Hashiba (19) in families with long QT syndrome.

Zareba et al. (7) have recently reported that, analogous to the presently described age-gender differences in QTc interval, cumulative cardiac event rates among blood relatives with long QT syndrome become attenuated in males after puberty. This phenomenon underlies the observed "greater" risk of cardiac events during adulthood in women compared with men from long QT syndrome families (5–7).

Role of heart rate. We considered the possibility that changes in heart rate (i.e., preferential slowing in men yielding smaller QTc values) might explain the age-gender difference in QTc evolution. Both women and men, however, exhibited slower heart rates relative to the children in our study.

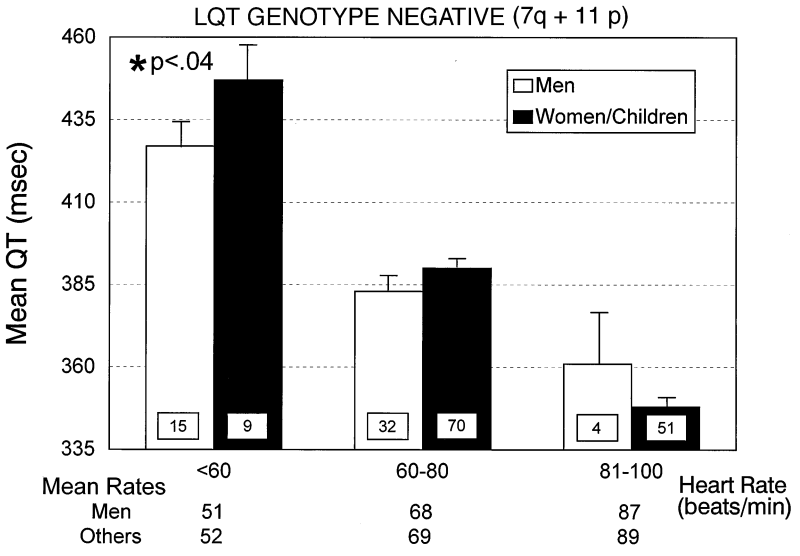

Figure 3. Mean absolute QT values in men (**open bars**) versus women and children combined (**solid bars**) for three ranges of heart rate in genotype-negative blood relatives pooled from 7q- and 11p-linked families with long QT (LQT) syndrome. Number of blood relatives for age-gender group and heart rate range is shown near bottom of bars; SEM indicated above bars.

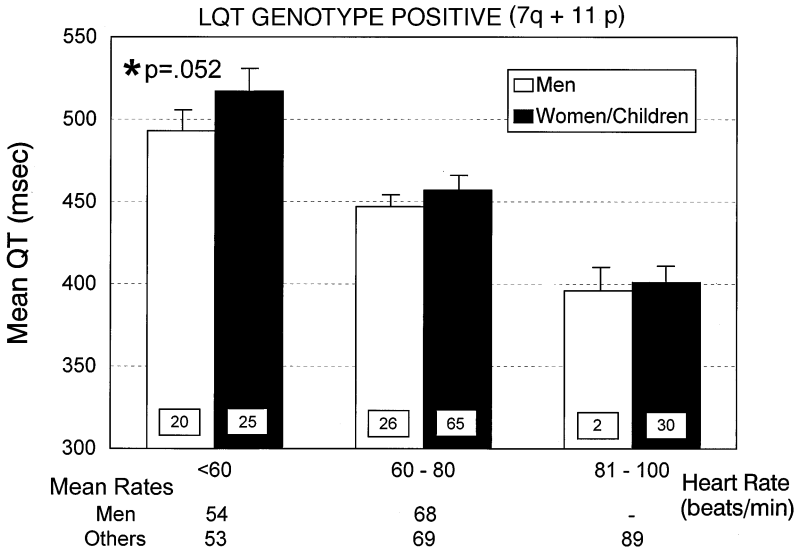

Figure 4. Mean absolute QT values in men (**open bars**) versus women and children combined (**solid bars**) for three ranges of heart rate in genotype-positive blood relatives pooled from 7q- and 11p-linked families with long QT (LQT) syndrome. Format and abbreviations as in Figure 3.

Moreover, multivariate analysis documented a significant, albeit modest, effect on QTc interval of age-gender group (men vs. women and children), even after taking into account genotype status, with a lesser contribution of heart rate, per se. Additional multiple regression analysis showed that age-gender group was a statistically significant predictor of absolute QT interval, as well, independent of (but exerting a smaller influence than) heart rate or genotype.

Analysis of mean QT values over specific heart rate ranges (Fig. 3 and 4) revealed that the shorter QT values in men were mainly evident at slow rates, i.e., <60 beats/min, for both genotype-negative and -positive blood relatives. This intriguing observation is consistent with preliminary findings recently reported in normal subjects (30). Moreover, mathematical analysis by Rautaharju et al. (27) of an optimal QT prediction formula (fitted to a large group of normal subjects) revealed that the instantaneous sensitivity of QT interval to changes in heart rate, although greater in both genders at slower rates, was reduced in men compared with women to a degree more pronounced at a heart rate of 40 beats/min than at 125 beats/min. The nature of the gender difference in the QT–heart rate relation, as suggested by these various studies, is of potential physiologic importance because relatively blunted QT prolongation at slow rates could be especially helpful in defending men against torsade de pointes, an arrhythmia facilitated by bradycardia (31,32).

Table 6. Multiple Regression Analysis of Variables Predictive of Absolute QT Interval in Pooled Genotypically Characterized Long QT Syndrome Families Linked to Chromosome 7q (HERG) or 11p (KVLQT1)

Variable	Contribution to Model R^{2}*	Regression Coefficient (beta)	SE (beta)	p Value
Heart rate	0.554	−0.0019	0.0001	<0.001
Genotype (+/−)	0.234	0.1166	0.0111	<0.001
Genotype–heart rate interaction	0.012	−0.0007	0.0001	<0.001
Age-gender group (adult men/others)	0.003	0.0092	0.0036	0.01

*Model R^{2} = 0.803.

Study limitations. In our study, age-gender differences in QTc interval were analyzed using ECGs obtained at a single point in time from multiple individuals of a particular age and gender. It would be important to determine whether our findings can be confirmed in large longitudinal studies in which QTc intervals of individuals are tracked from childhood into adulthood. Interestingly, Hashiba (19) has already published serial ECG tracings documenting QTc shortening during teenage years in three affected males from long QT syndrome families.

At present, our findings with regard to congenital long QT syndrome can be considered applicable only to the 7q- and 11p-linked variants. The type of analysis used herein needs to be extended to other chromosome (e.g., 3p)-linked families once larger groups of such blood relatives are identified.

Implications. From a mechanistic standpoint, the present findings, in tandem with other recent observations (7,15), necessitate a revision in our thinking regarding the gender disparity seen in adults with respect to cardiac repolarization. Rather than focusing on the relative lengthening of QTc interval and the greater propensity toward torsade de pointes (from a variety of causes) in women, we need to shift our attention to address the question of what factor(s) in men act to shorten the QTc interval and exert a protective effect against the occurrence of torsade de pointes. This approach is also indirectly supported by the similar propensity to *d,l*-sotalol–induced JTc prolongation and torsade de pointes in women of pre- and postmenopausal age (2,33), arguing against a contributory role for estrogen.

Androgens logically merit investigation as candidate factor(s) that might foster blunted QT prolongation responses in men.

Recent experimental data, indeed, suggest a lesser degree of quinidine-induced QT prolongation in dihydrotestosterone- versus estradiol-pretreated ovariectomized rabbits (34). Conceivably, androgens might alter the "mix" of cardiac ion channels that are expressed, analogous to the observed alteration by testosterone of myosin heavy chain isoform expression in rat heart (35) and induction by diethylstilbesterol of the potassium channel protein *Isk* in rat uterus (36). More basic research is needed to explore this promising avenue of investigation, as well as other potential mechanisms for the gender disparity that exist in the pathophysiology of cardiac repolarization.

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