Title: The effect of age and gender on the QTc-interval in children and adolescents with type 1 and 2 Long-QT syndrome

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Abstract

Background

In congenital Long-QT Syndrome (LQTS) age, gender and genotype have been associated with cardiac events, but their effect on the QTc-interval has never been established. We therefore aimed to assess the effect of age and gender on the QTc-interval in children and adolescents with type 1 (LQT1) and type 2 (LQT2) LQTS.

Methods and Results

QTc-intervals of 12-lead rest electrocardiograms were determined and trends over time were analyzed using a linear mixed-effects model. The study included 278 patients with a median follow-up of 4 years (IQR 1-9) and a median number of 6 (IQR 2-10) electrocardiograms per patient. LQT1 and LQT2 males both showed QTc-interval shortening after the onset of puberty. In LQT2 males this was preceded by a progressive QTc-interval prolongation. In LQT1, after the age of 12 years, males had a significantly shorter QTc-interval than females. In LQT2, during the first years of life and from 14-26 years, males had a significantly shorter QTc-interval than females. On the contrary, between 5-14 years, LQT2 males had significantly longer QTc-interval than LQT2 females.

Conclusions

There is a significant effect of age and gender on the QTc-interval in LQTS, with a unique pattern per genotype. The age of 12-14 years is an important transitional period. In the risk-stratification and management of LQTS patients, clinicians should be aware of these age-, gender- and genotype-related trends in QTc-interval, and especially the important role of the onset of puberty.

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Introduction

Congenital long-QT syndrome (LQTS) is a heterogeneous group of inheritable cardiac repolarization disorders, with a predisposition to malignant ventricular arrhythmias that can precipitate syncope, sudden cardiac arrest (SCA) or sudden cardiac death (SCD).[1-3] The delayed repolarization results in a prolongation of the QT-interval corrected for the heart rate (QTc) on the electrocardiogram (ECG). The most common types of LQTS are type 1-3 (LQT1-3), which are a result of mutations in potassium channel genes *KCNQ1 (I_{Ks})* and *KCNH2 (I_{Kr}),* or sodium channel gene *SCN5A (I_{Na})*,[4] respectively.

The genesis of LQTS-related cardiac events is not only dependent on the degree of QTc-interval prolongation. A complex influence of a variety of factors including age, gender and genotype is described. Children and adolescents constitute an especially important risk group.[5] In children, LQT1 males have a higher risk and an earlier onset of cardiac events compared to LQT1 females,[6-8] but no gender-related differences in LQT2 and LQT3 children have been described.[6, 7, 9] After the onset of puberty changes occur in the risk for cardiac events, with an increased risk in LQT2 females compared to LQT2 males, and no gender-related differences in LQT1 and LQT3 patients.[6-9] Unfortunately, there are no data on the influences of age, gender and genotype on the QTc-interval other than comparisons of baseline QTc-intervals between categorical age groups.[7, 8, 10, 11]

The onset of puberty plays an important role in gender-related differences in the risk for cardiac events in especially LQT1 and LQT2 patients, which is not seen in LQT3 patients. We hypothesize that the onset of puberty also effects gender-related differences in QTc-interval. Therefore our objective was to assess sequential QTc-interval data from a large cohort of children and adolescents with LQT1 and LQT2, in order to gain insight in the trend of the QTc-interval in LQTS.

Methods

Study population

A multicenter retrospective cohort study was performed including LQT1 and LQT2 patients born after January 1st 1985. LQTS type was defined as a confirmed pathogenic mutation in either KCNQ1 or KCNH2, detected using conventional methods. Consecutive patients from five medical centers in The Netherlands were included until June 2015. Patients were excluded if they were double mutation carriers or a known compound heterozygote. The study was approved by the Academic Medical Center Review Board.

Data collection and management

Patients characteristics were collected and all 12-lead rest ECGs were digitalized, blinded and manually analyzed by one investigator (SV) using the open source image processing program Image J 1.50i [National Institutes of Health, USA]. The QT-intervals of three consecutive complexes and their preceding RR-intervals were measured in a period without a marked sinus arrhythmia. The duration of the QT-interval was determined from the beginning of the QRS-complex to the end of the T wave using the tangent method in lead II or V5. If the QT-interval could not be determined using lead II and V5, one of the remaining leads was preferably used in all ECGs of that individual patient. The QTc-interval was calculated with Bazett's correction formula[12] averaging the three consecutive complexes.

Baseline ECGs were excluded from analysis if they were made during the first month after birth, during hospital admission or in the presence of QT prolonging drugs as registered on CredibleMeds®, as were ECGs with ventricular pacing or atrial- and ventricular arrhythmias.

Follow-up duration was defined as the time period in years from the date of the first ECG until the date of the latest.

Control population

The trends in QTc-interval for LQTS patients were compared to the trends for healthy controls. To gather information on trends in healthy controls, we used two different sources. Firstly, we compared the trends in QTc-interval for LQTS patients to the normal median values reported in Dutch children[13] and adolescents.[14] Age- and gender-dependent normal non-serial values were obtained

from population-based prospective cohorts and medical students. Details on the exact measurements are described elsewhere,[13, 14] but in short, the QT-interval was measured by the Modular ECG Analysis System (MEANS)[15] and QTc-interval was calculated using the Bazett's correction formula.[12]

Secondly, we used the original data from a previous study on the cut-off values for QT-intervals in Japanese children and adolescents.[16] In this study, serial QT- and RR-intervals were obtained at the age of 6, 12 and 15 years in 1240 males and 1338 females. Three consecutive QT- and RR-intervals were measured using the tangent method and averaged. The QTc-interval was calculated using the Bazett's correction formula.[12] Further details of this study are described elsewhere.[16]

Statistical analysis

All data were manually entered into a SPSS statistics database version 20.0 and analyzed with R version 3.1.3. We considered four subgroups: LQT1 males, LQT1 females, LQT2 males and LQT2 females. Characteristics of the study population were presented as frequencies (percentage) for categorical variables, mean (± standard deviation; SD) for continuous variables with an approximately symmetric distribution and median (Interquartile range; IQR) for continuous data with a skewed distribution. Binary data between two groups were evaluated using a Chi-square test.

We estimated average age trends in QT-interval, heart rate (HR) and QTc-interval using a linear mixed-effects model. A mixed-effects model takes account of repeated measurements per patient over time; the number and timing of measurements may vary per patient. To avoid selection bias, all patients with at least one ECG were included in the analysis.[17] The QTc-interval was allowed to vary smoothly by age via restricted cubic splines. Trends were allowed to differ by gender. The onset of puberty was set at 11.5 years in males and 10.7 years in females.[18] We compared changes between birth an onset of puberty, as well as between onset of puberty and 20 years. Sampling uncertainty was quantified via 95% confidence intervals (CI) and p-values. A p-value < 0.05 was considered to be statistically significant.

A sensitivity analysis for the trend in QTc-interval in the presence of constant medication conditions was performed for (I) β-blocker therapy, (II) propranolol treatment and (III) both QTc prolonging[19] and QTc shortening therapy. A more detailed description of the mixed-effects model and the sensitivity analysis is provided in the Supplemental material.

The trends in QTc-interval for both control populations were differentiated by gender. The Dutch data published by Rijnbeek et al.,[13, 14] was plotted as absolute median values and the Japanese data was analyzed using a linear mixed-effects model with age as a factor.

Results

Population Characteristics

A total of 343 patients were eligible for the study. Sixty-five patients (19%) were excluded, either because they had no ECG (n=63), or only one ECG that was made within 28 days after birth (n=2). These 65 patients were generally referred for genetic testing alone and follow-up was done in another hospital. The resulting cohort comprised 278 patients from 147 families, which were all included in the analysis. These patients had a total of 2367 ECGs of which 251 ECGs were excluded from analysis, mainly because they were made during hospital admission (61%), leaving a total of 2116 ECGs for analysis.

Baseline clinical characteristics of all four groups are shown in Table 1. The median age at presentation for the total cohort was 8 years (IQR 3-14 years), and most patients were diagnosed as a consequence of family screening (80%). Five percent was symptomatic before presentation, but these patients did not differ in baseline QTc-interval duration from asymptomatic patients (p=0.997).

Follow-up

Fifty-four patients had only one ECG (19%). All were referred for genetic testing and follow-up was done elsewhere. Genetic testing was most often performed in the context of family screening (76%); four patients (7%) had a SCA. One of these patients had a severe postanoxic encephalopathy and follow-up was discontinued at the request of the parents. There was no difference with regards to the number of probands (22% versus 19%, p=0.77) and the percentage of symptomatic patients at presentation (8% versus 4%, p=0.46) between patients without follow-up and patients with follow-up. Therefore, the patients without follow-up were considered to be a random sample of the total population and we assumed that data were missing at random.

Follow-up data of the 224 patients is shown in Table 2. Median follow-up duration was 5 years (IQR 2.5-10 years) with a median number of 8 ECGs (IQR 4-12 ECGs) per patient. Eleven patients (5%) had a cardiac event during follow-up. One of these patients (LQT2 female) had both symptoms at baseline and during follow-up. Most of the patients (88%) were on β-blocker therapy during follow-up.

Thirty-seven patients had a set of ECGs during the pubertal period; from 8 years to 14 years of age (7 LQT1 males, 10 LQT1 females, 10 LQT2 males and 10 LQT2 females). These patients showed no differences in number of probands (8% versus 22%, p=0.09), symptomatology at

presentation (5% versus 5%, p=1.00) or symptomatology during follow-up (8% versus 3%, p=0.37) compared to the other follow-up patients. Therefore, this group was considered to be a random sample of the total study population with respect to trends in QTc-interval during puberty.

Age-related changes in QTc-interval

Individual and average age-related changes in QTc-interval for LQT1 males, LQT1 females, LQT2 males and LQT2 females are shown in Figure $1_{A,C,B,D}$. The age-related changes in QTc-interval were not statistically significantly different between symptomatic and asymptomatic patients for both LQT1 and LQT2 (p=0.52 and p=0.15, respectively), however note that the number of symptomatic patients was small. In addition, there was also no statistically different between probands and family members (LQT1 p=0.30 and LQT2 p=0.69).

Age-related changes differed by gender in LQT1 patients (p=0.01). In LQT1 males, age significantly influenced the QTc-interval (p=0.02). From birth to the onset of puberty, the duration of the QTc-interval remained unchanged (p=0.57), after the onset of puberty the QTc-interval shortened until the age of 20 years (p=0.02). In LQT1 females no influence of age on the QTc-interval was seen (p=0.30). LQT2 males showed an evident change in QTc-intervals over time (p<0.0001) with QTc-interval prolongation between birth and the onset of puberty (p<0.0001) and QTc-interval shortening thereafter (p<0.0001). In LQT2 females, there was also a significant influence of age on the QTc-interval (p=0.003), but with a different pattern than in LQT2 males (p<0.001). From birth to the onset of puberty the QTc-interval duration tended to shorten (p=0.10), after which the QTc-interval duration increased before it decreased again to the age of 20 years (p=0.29).

All four groups showed significant age-related changes in HR and QT-interval, with a higher HR before puberty compared to the HR after puberty and the opposite effect in QT-intervals (data provided in the Supplemental material).

Sensitivity analysis

In the sensitivity analyses, ECGs excluded for LQT1 and LQT2 respectively were for (I) β-blocker therapy 188 (20%) and 227 (20%), (II) propranolol treatment 166 (17%) and 110 (10%), and (III) both QTc prolonging and QTc shortening therapy 19 (2%) and 76 (7%). All sensitivity analyses showed no relevant changes in the results.

Gender differences in age-related changes in QTc-interval

The age-related changes in QTc-interval for males and females as described above were combined per genotype to evaluate the gender differences (Figure $1_{E,F}$). LQT1 patients showed no gender-related differences in QTc-interval during the first twelve years of life. After the age of 12 years, LQT1 males had a significantly shorter QTc-interval compared to LQT1 females. There were no gender differences in age-related changes in HR and QT-interval.

In LQT2 patients a significant gender-related difference in QTc-interval was present during the first two years of life, during which LQT2 males had a shorter QTc-interval compared to LQT2 females. Between the age of 5 to 14 years, the QTc-interval in males becomes longer than in females and after the age of 14, again the QTc-interval in males becomes shorter than in females. With regard to gender differences in trends of HR and QT-interval, no gender differences were observed in HR for both genotypes, but longer QT-intervals were seen in LQT2 males between the ages of 6-11 years compared to LQT2 females. There were no gender differences in QT-interval in LQT1.

Trends in QTc-interval between healthy controls and patients with LQTS

The median QTc-intervals for multiple age groups as described by Rijnbeek et al.[13, 14] were shorter compared to the averaged QTc-interval in both the LQT1 and LQT2 patients (Figure 1). In these Dutch controls there was a relatively constant trend in QTc-interval with no gender-differences except between the ages of 1-3 months ($p<0.05$).[13]

Japanese controls showed a shorter averaged QTc-interval compared to the median QTc-intervals of the Dutch controls, as well as for the averaged QTc-interval of both LQT1 and LQT2 patients (Figure 1). Age significantly influenced the QTc-interval in these controls ($p<0.0001$), and the age-related change differed by gender ($p<0.0001$). At the age of 12 years, both males and females had a significant longer QTc-interval than at 6 years ($p<0.0001$). At the age of 15 years, both males and females had a significant shorter QTc-interval than at 12 years ($p<0.0001$). Males had shorter QTc-intervals at the ages of 12 and 15 years compared to females.

Discussion

Main findings

The present study is the first to analyze unique data of serial QTc-interval measurements in a large cohort of children and adolescents with LQT1 and LQT2, and has three major findings. Firstly, both LQT1 and LQT2 males show significant QTc-interval shortening after the onset of puberty. Secondly, in LQT2 males this is preceded by a progressive QTc-interval prolongation. Thirdly, the age of 12-14 years is an important transitional period where differences between males and females for both genotypes are seen, ages corresponding with the onset of puberty.

Age- and gender-related changes in QTc-interval in LQTS

Prior studies reported age-related changes in QTc-interval of both LQTS males and females by comparing children to adults. In LQT1 patients, male children showed longer QTc-intervals compared to male adults, and conflicting results were described for LQT1 females.[7, 11] Zareba et al.[7] reported longer QTc-intervals in female children compared to female adults, whereas Ozawa et al.[11] found no age-dependent changes. Our findings in LQT1 males are in line with these previous reports, and in agreement with the findings of Ozawa et al.,[11] observing no age-dependent changes in LQT1 females.

In LQT2 patients Zareba et al.[7] and Ozawa et al.[11] both showed no age-related changes in males and shorter QTc-intervals during childhood compared to adulthood in females.[7, 11] This is in contrast to the results in this study, where LQT2 males have shorter QTc-intervals after puberty and LQT2 females have no significant change in QTc-interval during adolescence.

Differences in QTc-interval between males and females have only been reported in patients above the age of 13-15 years.[7, 11] In LQT1 patients, females had either a longer QTc-interval compared to males,[10, 11] or no gender-related differences were found.[7] In the present study we also found that LQT1 females have a longer QTc-interval compared to LQT1 males after the age of 12 years. In LQT2 patients, consistent with previous studies,[7, 10, 11] we also demonstrated that after the second decade the QTc-interval in females is longer than in males. However, in contrast to observations in these previous studies, we did find gender-related differences in LQT2 patients during

childhood showing a significantly shorter QTc-interval in males than females during the first years of life and opposite, between 5-14 years, a longer QTc-interval in males than females.

This discrepancy between our findings and other studies may be explained by the methodology that was used. The previous studies compared median baseline QTc-intervals between dichotomous age groups, and did not take individual age trends into account. These aspects may have masked age- and gender-related differences in QTc-intervals. The same holds for the trend in QTc-interval in the Dutch controls. These controls showed shorter QTc-intervals compared to LQTS patients, but age and gender-related differences were not seen.

Sex hormones

Our findings on age- and gender-related changes in QTc-intervals for both LQTS and Japanese controls are most likely the result of changes in sex-specific hormones. Both clinical observational and animal studies have shown a QTc-interval shortening due to endogenous testosterone and progesterone.[20] Endogenous estrogen lengthens the QTc-interval in animal models.[20] Concentrations of sex hormones in children are influenced by the activity of the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis is active during the (1) mid-gestational period in the fetus, (2) first months of life and (3) pubertal period,[21] and therefore higher concentrations of testosterone and estrogen are found during these periods.

LQT1 patients have an impaired function of I_{Ks} channels, while LQT2 patients do not.[4] Since testosterone induces a dose-dependent shortening of the action potential duration through enhancement of I_{Ks} channels,[20] one could postulate that the shortening of the QTc-interval by testosterone is less pronounced in LQT1 males than in LQT2 males because the I_{Ks} channels may not be able to fully respond to the presence of testosterone. As a consequence, during periods of sudden changes in sex hormone concentrations (i.e. the first months of life and the onset of puberty), a marked QTc shortening would be expected in LQT2 males in contrast to LQT1 males. This may explain our findings in LQT2 males, which showed a shorter QTc-interval during the first year period and a more pronounced QTc shortening after the onset of puberty compared to LQT1 males. This hypothesis is strengthened by the fact that male Japanese controls showed a similar pattern to the LQT2 males.

Our data on LQTS females also indicates a differing sensitivity to changes in sex hormone concentrations between the genotypes studied, since an effect of age on the QTc-interval was only found in LQT2 females and Japanese female controls. Previous studies have shown that there is a significantly increased risk for cardiac events in LQT2 females compared to LQT1 females during periods of sudden changes in estrogen concentrations such as the postnatal period,[22, 23] onset of puberty,[6-9] puerperium period, first 9 months postpartum[24] and in the pre-, peri- and post-menopausal periods.[25] This data supports that LQT2 females may be more sensitive to changes in estrogen concentrations compared to LQT1 females, and this may be the underlying mechanism for our observations on the QTc-interval shortening in LQT2 females in the first months of life and the prolongation after the onset of puberty.

Cardiac events

In LQT1 patients, males have a higher risk during childhood and an earlier onset of cardiac events than females.[6-8] Our observations on gender-related differences in QTc-interval could not explain this gender difference in cardiac events during childhood based on the length of the QTc-interval, since this was similar in males and females. These study findings are in line with previous studies,[7, 10, 11] and therefore it has been suggested that the difference in risk for cardiac events between LQT1 males and females is related to the increased physical activity in males compared to females during childhood. Since LQT1 patients experience malignant ventricular arrhythmias more frequently during physical effort,[26] a presumably higher level of physical activity in males may contribute to a higher risk for cardiac events. We only measured the QTc-intervals on 12-lead rest EGCs, and could therefore have missed an impaired QTc response to a higher HR during physical effort in LQT1 males.

In LQT2 patients, a higher risk for cardiac events is found in LQT2 females after the onset of puberty compared to males.[6, 7, 9] Based on the findings in this study, this could be explained by a longer QTc-interval in females.

Modulating factors

We have considered factors that may have influenced our findings on age and gender differences in QTc-intervals. Firstly, in this study a higher HR is observed in children compared to

adolescents of both LQT1 and LQT2 patients. The Bazett correction formula has an optimal correction between 60 and 100 beats per minute (bpm), and correction at a slower or faster HR gives erroneous results with respectively over- and undercorrection.[27] A HR >100 bpm was observed from birth to an age of 3-4 years in both LQT1 and LQT2 patients. Therefore, QTc-intervals calculated with the Bazett correction formula may be underestimated in this specific time period. Gender related differences in HR were not observed in this study, which is consistent with previous studies.[7, 10] Stramba-Badiale et al.[28] however, showed that females have a more steep QT/RR ratio than males. With the assumption that this also applies to children, the use of the Bazett formula may cause a correction induced difference between genders.

Secondly, medication affecting the QTc-interval could have influenced the observed trends in QTc-interval in our study. We therefore performed three sensitivity analyses with the assumption that the introduction of these medicaments only has a short-term effect on the QTc-interval. Sensitivity analyses did not change the results with respect to age and gender related differences in QTc-intervals. However, we were not able to exclude possible effects of changes in the dose of the medication or the influences of specific types of medications on the QTc-interval.

Limitations of the study

Although this is the largest multicenter study to date examining trends in QTc-interval in LQT1 and LQT2 children and adolescents, it has the inherent limitation of being a retrospective study. A complete set of ECGs from 0-30 years was not available in all patients, and especially after the age of 25 years there are limited measurements. Missing ECGs are due to differences in the age of presentation, follow-up intervals, loss to follow-up and SCD. However, as long as those that were followed for a period can be seen as representative for the whole population of similar age, our linear mixed-effect model will provide unbiased estimated of the age trends. Our cohort seems to be a representative sample of the general LQT1 and LQT2 child population, since there were no indications that missing data were not at random. Finally, we were unable to investigate the trends in QTc-interval for specific mutations.

Conclusions

There is a significant effect of age and gender on the QTc-interval in LQTS, with a unique pattern per genotype. The age of 12-14 years is an important transitional period. In the risk-stratification and management of LQTS patients, clinicians should be aware of these age-, gender- and genotype-related trends in QTc-interval, and especially the important role of the onset of puberty. LQT2 patients should be closely monitored during periods of changes in sex hormone concentrations since they are more sensitive to these variations than LQT1 patients.

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Conflict of Interest Disclosures

None

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Table 1. **Baseline characteristics**

	All patients n=278	LQT1 males n=60	LQT1 females n=70	LQT2 males n=67	LQT2 females n=81
Presentation					
Family screening	220 (80%)	46 (77%)	50 (71%)	59 (89%)	65 (81%)
Syncope	26 (9%)	4 (7%)	11 (16%)	3 (5%)	8 (10%)
Near-drowning	3 (1%)	2 (3%)	1 (1%)	0 (0%)	0 (0%)
SCA	7 (3%)	1 (2%)	2 (3%)	1 (2%)	3 (4%)
Incidental*	9 (3%)	3 (5%)	4 (6%)	1 (2%)	1 (1%)
Other†	11 (4%)	4 (7%)	2 (9%)	2 (3%)	3 (4%)
Median age at presentation in years (IQR)	8 (3-14)	7.5 (3-12)	8 (3-14)	9 (4-14)	8 (4-15)
Symptomatic before or at presentation‡					
Near-drowning	7 (2%)	3 (5%)	4 (6%)	0 (0%)	0 (0%)
SCA	7 (3%)	1 (2%)	2 (3%)	1 (2%)	3 (4%)
Ventricular arrhythmias	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Median age first event in years (IQR)	11 (6.0-15.0)	11 (10.5-12.5)	7 (6.0-15.0)	0 (0-0)	16.5 (10.0-20.0)
Family history					
Negative	74 (28%)	11 (19%)	22 (33%)	16 (25%)	24 (33%)
Positive but not malignant	28 (11%)	13 (22%)	8 (12%)	3 (5%)	4 (5%)
Malignant‡	162 (62%)	35 (59%)	37 (55%)	45 (70%)	45 (62%)
Number of families	147	48	52	45	50
Probands	55 (20%)	14 (23%)	20 (29%)	7 (10%)	14 (17%)
Mean QTc in ms (±SD)	451 (±39)	444 (±33)	451 (±38)	453 (±48)	454 (±35)

SCA= Sudden Cardiac Arrest, IQR= Interquartile range, QTc= QT-interval corrected for heart rate, ms= milliseconds,

SD= Standard Deviation

* Incidental= Due to pre-operative screening or regular health exam

† Other= During the evaluation of specific symptoms i.e. palpitations, murmur, dyspnea, chest pain, near-syncope, dizziness or prenatal symptoms

‡ i.e. near-drowning, SCA or documented ventricular arrhythmias

460 **Table 2.** Follow-up

	All patients n=224	LQT1 males n=50	LQT1 females n=58	LQT2 males n=52	LQT2 females n=64
New events during follow-up					
Near-drowning	1 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
SCA	1 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Ventricular arrhythmias	9 (4%)	0 (0%)	4 (7%)	0 (0%)	5 (8%)
β-blocker therapy	188/213 (88%)	43/47 (91%)	53/58 (91%)	40/48 (83%)	52/60 (87%)
Device					
Pacemaker	3 (1%)	0 (0%)	0 (0%)	1 (2%)	2 (3%)
ICD	12 (5%)	1 (2%)	3 (5%)	2 (4%)	6 (9%)
Median age start β-blocker in years (IQR)	8 (5.0-13.0)	7 (4.0-11.5)	8 (3.0-12.0)	9 (7.0-13.0)	9 (6.0-14.0)
Median number of ECGs per patient (IQR)	8 (4-12)	6 (4-10)	8 (5-11)	8.5 (5-16)	7 (4-13)
Median follow-up duration per patient in years (IQR)	5 (2.5-10.0)	5 (3.0-7.0)	5 (3.0-9.0)	8 (4.0-11.0)	5 (2.0-10.0)

461 SCA= Sudden Cardiac Arrest, ICD= Implantable Cardioverter Defibrillator, IQR= Interquartile range

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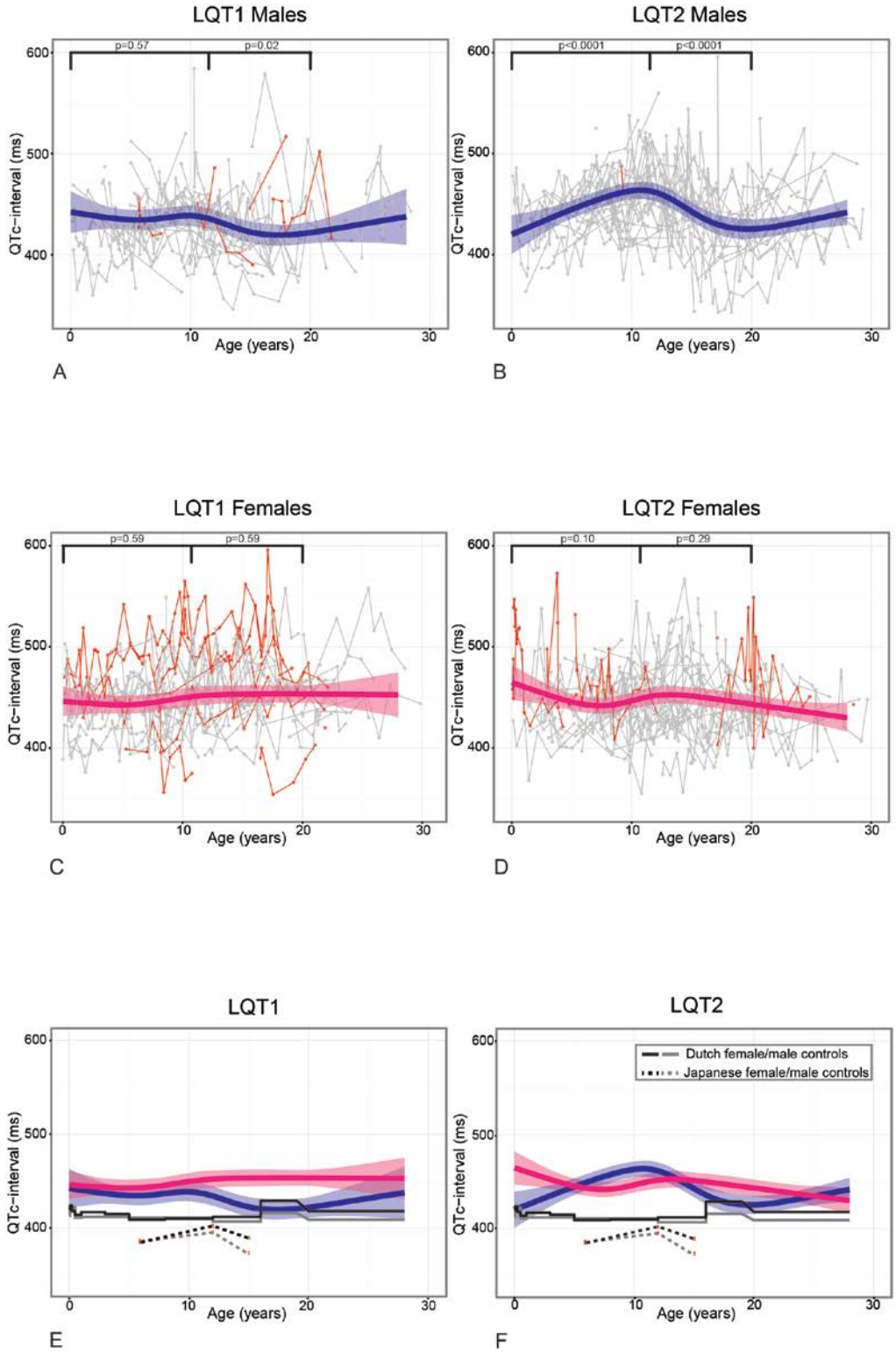

Figure 1. Age-related changes in QTc-interval in (A) LQT1 Males, (B) LQT2 Males, (C) LQT1 Females, (D) LQT2 Females, (E) LQT1 and controls and (F) LQT2 and controls. A-D: Dots are individual measurements and lines are individual trends. Symptomatic patients are shown in red. The 95% confidence intervals for the fitted model are shown. E-F: Lines of LQTS males and LQTS females combined per genotype. Blue lines are LQTS males and pink lines are LQTS females. Both Dutch and Japanese control males and females are also shown. Grey lines are control males and black lines are control females. The 95% confidence interval for the Dutch controls is not shown. The 95% confidence interval for the Japanese controls is too narrow to be visible.