High prevalence of four long QT syndrome founder mutations in the Finnish population

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Abstract

Aims—Long QT syndrome (LQTS) is an inherited arrhythmia disorder with an estimated prevalence of 0.01%–0.05%. In Finland, four founder mutations constitute up to 70% of the known genetic spectrum of LQTS. In the present survey, we sought to estimate the actual prevalence of the founder mutations and to determine their effect sizes in the general Finnish population.

Methods and results—We genotyped 6334 subjects aged 30 years from a population cohort (Health 2000 study) for the four Finnish founder mutations using Sequenom MALDI-TOF mass spectrometry. The electrocardiogram (ECG) parameters were measured from digital 12-lead ECGs, and QT intervals were adjusted for age, sex, and heart rate using linear regression. A total of 27 individuals carried one of the founder mutations resulting in their collective prevalence estimate of 0.4% (95% CI 0.3%–0.6%). The *KCNQ1* G589D mutation (n=8) was associated with a 50 ms (SE 7.0) prolongation of the adjusted QT interval (P=9.0×10^{-13}). The *KCNH2* R176W variant (n=16) resulted in a 22 ms (SE 4.7) longer adjusted QT interval (P=2.1×10^{-6}).

Conclusion—In Finland 1 individual out of 250 carries a LQTS founder mutation, which is the highest documented prevalence of LQTS mutations that lead to a marked QT prolongation.

Keywords

Epidemiology; ion channels; KCNH2; KCNQ1; long QT syndrome; QT interval

Introduction

Long QT syndrome (LQTS) is an inherited arrhythmic disorder characterized by prolonged QT interval on the electrocardiogram (ECG) and a risk for ventricular tachyarrhythmias and sudden death (1-3). A total of ten genes and several hundreds of mutations have been identified to underlie the disorder (2), most of them affecting the function of cardiac ion channels. In addition to the strong effects of disease-causing mutations, several common variants in the LQTS genes have been shown to prolong QT interval duration and predispose to the clinical manifestations of the disorder (3).

Key messages

- This is the first attempt to estimate the prevalence of LQTS at the population level using molecular methods.

- The reported prevalence estimate of 0.4% is considerably more than the generally estimated prevalence of LQTS (0.01%–0.05%) in other populations.

- The four Finnish LQTS founder mutations lead to a substantial 22–50 ms QT prolongation also at the population level and could thus mark individuals at risk for arrhythmias.

LQTS is assumed to be a rare disorder with a recent prevalence estimate of 1/2000 (4). Approximately 75% of genotyped LQTS patients carry a mutation in either *KCNQ1, KCNH2 (HERG)*, or *SCN5A* gene that are responsible for LQTS subtypes 1–3 (5). In Finland, four previously described mutations, including G589D and IVS7-2A>G in the *KCNQ1* gene and *KCNH2* L552S and *KCNH2* R176W, account for up to 70% of the known genetic spectrum of long QT syndrome (6). The aim of this survey was to estimate the prevalence of the LQTS founder mutations in Finland using an unselected population-based Health 2000 sample and to determine whether these mutations are associated with QT interval prolongation at the population level.

Methods

Study population

The study population consisted of a cross-sectional cohort of 8028 individuals drawn from the Finnish Population Information System (http://www.vaestorekisterikeskus.fi/vrk/home.nsf/www/populationinformationsystem) for the Health 2000 survey. The two-stage stratified cluster sample was collected between September 2000 and June 2001 and is representative of the entire Finnish population of 30 years and more (www.ktl.fi/health2000) (7). DNA samples were collected from 6334 individuals, and digital standard 12-lead ECGs were available from 6295 study participants (78% of the original sample). The prevalence estimates with 95% confidence intervals were calculated from the weighted genotyped study population (n=6334) as described earlier (7).

When the QT-prolonging effect of each mutant allele was specifically investigated, subjects with complete left or right bundle branch block (n=143), QRS 120 ms (n=205), atrial fibrillation or flutter (n=94), pacemaker (n=12), or using a potentially QT-altering medication (n=1064), including digoxin, were excluded from the calculations. A drug was considered to potentially prolong the QT interval if it was listed in any of the four categories at www.qtdrugs.org (accessed November 2006). In addition, we excluded the following agents that might also affect ventricular repolarization: carbamazepine, flupentixol, levomepromazine, me-floquine, olanzapine, oxcarbazepine, periciazine, sertindole, and

trazodone. This study population used for QT interval analyses included 5068 individuals free of exclusions. Clinical characteristics, including medications, prior heart failure, history of myocardial infarction, prevalent diabetes, and smoking status, were determined as described previously (7). The occurrence of juvenile (<40 years) deaths in the first-degree relatives of each study participant was assessed using an investigator-administered questionnaire (7). The study was performed according to the declaration of Helsinki and was approved by the Ethical Committees of the Hospital District of Helsinki and Uusimaa and the National Public Health Institute. Written informed consent was obtained from the participants.

QT interval measurements

Digital standard 12-lead ECGs were recorded using Marquette MAC 5000 (GE Marquette Medical Systems, Milwaukee, WI, USA), and a digital median QRS-T complex was used for analyses. We used QT Guard software (GE Marquette Medical Systems, Milwaukee, WI, USA) to measure heart rate, and custom-made software for QT interval measurements. These measurements were based on a previously described and validated algorithm (8). The software calculates QT interval from QRS onset to T wave offset in each lead. A single observer (KP) reviewed all measurements in a blinded fashion, and the mean QT interval of all 12 leads was used for final analyses. The intraobserver coefficient of variation was 0.7% for the mean QT interval in repeated ECG measurements in our recent study (9), and the same measurement methods were used also in the present survey. In addition, the QT intervals of the founder mutation carriers were measured manually by a single cardiologist (HS) in order to allow comparison with the same measurement technique used by HS among clinical LQTS samples. The measured QT intervals were corrected for heart rate using Bazett's formula (10). Left ventricular hypertrophy was assessed as a dichotomous variable based on the Sokolow-Lyon voltage >35 mm (11) and/or gender-adjusted Cornell voltage duration product >2440 mmms (12).

Genetic analyses

Genotyping for the four Finnish founder mutations was performed using Sequenom MALDI-TOF mass spectrometry (MassArray Compact Analyzer, Sequenom Inc., San Diego, USA). Sequences were evaluated in the ProxSNP and PreXTEND software (www.realsnp.com), and the reactions were designed utilizing Sequenom Assay Designer 3.1 software. Genotyping was performed with the iPLEX method for *KCNQ1* (NM_000218) G589D G/A and IVS7-2A>G and *KCNH2* (NM_000238) L552S T/C, and with homogeneous MassEXTEND method for *KCNH2* R176W C/T according to standard protocols. The polymerase chain reaction (PCR) primer and extension primer sequences are available by contacting the authors. Reactions were tested with 32 DNAs prior to genotyping. Previously identified heterozygous DNA samples from an earlier study (6) served as positive controls in the genotyping process. The genotyping calls were made using Spectro-Analyzer 3.4 software. The heterozygous samples were confirmed by direct sequencing in forward and reverse directions using an ABI 3730 Automatic DNA sequencer (Applied Biosystems, Foster City, MA, USA) and the previously described primer sequences (6,13-15).

Statistical analyses

Histograms of all the variables were inspected for normality. We assessed correlations of crude values of sex-pooled and sex-specific age, heart rate (RR interval), and QT intervals. Using stepwise linear regression model, we adjusted the QT intervals for age, sex, and RR-interval (16,17) and determined the beta coefficient, two-tailed *P*-value, and partial R^2 of the covariates in the model. In addition, we tested additional possible covariates, i.e. left ventricular hypertrophy, history of myocardial infarction, heart failure, prevalent diabetes,

smoking status, diuretic usage, and geographical area, for a possible additional explanatory role in the model. As these covariates accounted for less than 1% of the variation of QT interval in the study population, did not reach strong statistical level of significance (P>0.001), and in order to use a measure comparable to other studies, we derived the QT residuals from the age-, sex-, and heart rate-adjusted model. The histograms of output residuals were reviewed for normality (skewness 0.37, SE 0.03, kurtosis 1.21, SE 0.07). Statistical analyses were performed using SPSS 13.0/15.0 (SPSS Inc., Chicago, Illinois, USA). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The characteristics of the initial study population have been described elsewhere (7). The mean age was 51±14 years. Women (53%) featured longer mean QTc (402±20 ms, 95% CI 401.2–402.8 ms) than men (389±22 ms, 95% CI 387.8–389.6 ms), P<0.001. A total of 120 (2.4%) subjects had a QTc interval greater than 440 ms (18), and 9 of them (0.2%) featured a QTc longer than 470 ms (18). The subjects on QT-prolonging drugs had a 4.0 ms longer QT interval compared to those study participants without such medication.

Successful genotyping calls were obtained for 97.6%–99.9% of the DNA samples, and 6263 study participants were successfully genotyped for all four founder mutations. No homozygous nor compound heterozygous carriers were identified in the study population. A total of 27 individuals were heterozygous carriers of one of the four Finnish founder mutations, *KCNQ1* G589D (*n*=8), *KCNQ1* IVS7-2A>G (*n*=1), *KCNH2* L552S (*n*=2), or *KCNH2* R176W (*n*=16). The sex distribution was similar in the four groups of founder mutation carriers. Collectively, these four founder mutations have a prevalence estimate of 0.4% (95% CI 0.3%–0.6%) in the Finnish population.

Table I summarizes the clinical characteristics of the founder mutation carriers and non-carriers in the Health 2000 survey, after exclusion of one carrier of *KCNQ1* G589D (QTc 438 ms) and one carrier of *KCNQ1* IVS7-2A>G (QTc 409 ms) who were treated with a potentially QT-prolonging drug (salbutamol and terbutaline, respectively). None of the 27 individuals possessed other exclusion criteria. The differences in the QTc intervals between founder mutation carriers and non-carriers are illustrated in Figure 1.

The mutant allele A of *KCNQ1* G589D was identifiable in eight individuals in heterozygous form and was found to be associated with a 50.5 ms (SE 7.1, 2.7 SD, P=8.99×10^{-13}) increase of the QT interval when compared to mutation non-carriers. A total of 16 study participants carried the minor *KCNH2* R176W allele and showed a 22.2 ms (SE 4.7, 1.2 SD, P=2.15×10^{-6}) longer QT interval compared to mutation non-carriers. No systematic ascertainment of personal or family history of arrhythmia symptoms was undertaken as part of the Health 2000 population-based survey. One mutation carrier, a person with *KCNQ1* G589D and a QTc of 520 ms, had previously been symptomatic. None of the parents of the 27 mutation carriers had died before 40 years of age. Ten (37%) founder mutation carriers had siblings who had suffered from juvenile (<40 years) death, but the difference to the corresponding frequency in mutation non-carriers (*n*=1541, 25%) was not statistically significant (P=0.14).

It was pertinent to exclude the possibility that the high prevalence estimate would have resulted because of enrolment of a given geographic area showing an exceptional clustering of a specific founder mutation. Therefore, we compared the distribution of founder mutation carriers, first, in the Health 2000 material, and second, in the updated material of clinical LQTS indexes (described in reference (7), and supplemented by additional cases by H.

Swan). The geographical distribution of the four founder mutations in these two groups are shown in Supplementary Figure 1 (http://www.informaworld.com/annmed). The grey areas represent municipalities enrolled for the Health 2000 study. These maps indicate that the four founder mutations are widely distributed in Finland, and no preferential area enrichment affects the Health 2000 study in this respect. The only exception is the *KCNQ1* IVS7-2A>G mutation that appears to be clustered to the southern Finland, as based on the clinical index material. As only one Health 2000 study participant carried the *KCNQ1* IVS7-2A>G, its contribution to the prevalence calculations is negligible.

Discussion

Using a large, epidemiological study cohort of more than 6000 individuals, we report a 0.4% prevalence of disease-causing LQTS founder mutations in Finland. This is considerably more than the generally estimated prevalence of 0.01% (19) to 0.05% (20) in other populations and may reflect the special genetic composition of the Finnish population. Increasing evidence suggests that these founder mutations may be enriched in the isolated Finnish population as they were found to be relatively frequent in a subset of acquired long QT syndrome (21). Because genotyping was targeted only to these four founder mutations and the Health 2000 Study did not include subjects younger than 30 years old, the actual prevalence of disease-causing LQTS mutations in Finland is likely to be even higher.

Previously, we have reported that the *KCNQ1* G589D is associated with a mean QTc of 462±38 ms (*n*=508), *KCNQ1* IVS7-2A>G with a QTc of 470±31 ms (*n*=55), *KCNH2* L552S with a QTc of 463±45 ms (*n*=90), and *KCNH2* R176W with a mean QTc of 459±40 ms (*n*=30) in clinical LQTS families (6). In addition to the prolongation of the QTc interval, these four mutations have been associated with symptoms, i.e. syncopal spells or sudden death, in 23%–38% of the mutation carriers among previous clinical samples (6) thus being sufficient to cause a life-threatening form of LQTS. In the present epidemiological data set, the mean QTc intervals are slightly shorter than in our previous report on the clinical sample and may reflect an unavoidable bias in clinical settings. For comparison, we also made manual QTc measurements in the founder mutation carriers of the present study; the QTc intervals in the founder mutation carriers were 444±10 ms for *KCNQ1* G589D, 456±12 ms for *KCNH2* L552S, and 433±27 ms for *KCNH2* R176W. The patient population ascertained on the presence of overt syncope or arrhythmia may possess other uncharacterized genetic modifier factors that contribute to the QT prolongation and thus to the clinical manifestations of the disorder.

The Finnish type of *KCNQ1* founder mutations has not to our knowledge been described in other patient populations. *KCNH2* L552S has been identified in a single Caucasian family (22) as a disease-causing LQTS mutation. In contrast, the *KCNH2* R176W has been reported elsewhere as an innocent polymorphism with a minor allele frequency of 0.3%–0.5% in the healthy white population (19,23). In Finland, the variant was previously detectable in 0.9% (3/317) of randomly collected blood donors, but it was significantly enriched in LQTS patients with an 8% genotype frequency among LQTS probands (6). At present, we have identified the *KCNH2* R176W mutation in 112 LQTS patients, of which 18 (16%) are symptomatic (Swan et al., unpublished observations). Up to 40% of male mutation carriers (16 of the 40 men free of QT-affecting medication) have QTc over 440 ms. Similarly, 22% (12/55) of female R176W carriers show a QT prolongation over 460 ms (Swan et al., unpublished observations). Furthermore, the *KCNH2* R176W was identified in six *KCNQ1* founder mutation carriers from four LQTS1 families (24). Five patients with compound *KCNQ1* G589D and *KCNH2* R176W mutations had a mean QTc of 473±30 ms as opposed to the QTc of 457±33 ms in *KCNQ1* G589D carriers (*n*=371) alone (24). In addition, four (67%) of these compound heterozygous patients were symptomatic (24).

However, until now the actual effect size of this variant in the general population has remained uncertain.

Recently, it was shown that up to one-third of the variation in the QT interval is heritable (25,26). The growing interest in understanding genetic modulation of cardiac repolarization has led to the identification of gene variants that affect QT interval duration in unselected population-based samples (27-31). However, the effects of common gene variants on QT interval duration have remained relatively modest in these epidemiological surveys (28-30). In the present study, the *KCNH2* R176W is shown to be associated with a 22 ms prolongation of the age-, sex-, and heart rate-adjusted QT interval. This is considerably stronger than the previously presented effect sizes among common gene variants (28-30) and, along with the data on clinical *KCNH2* R176W samples, strongly supports the role of the *KCNH2* R176W in predisposing to repolarization-related arrhythmogenesis, at least in the Finnish population.

Previous *in vitro* experiments of mutant channels provide further evidence of the pathogenicity of the Finnish LQTS founder mutations. *KCNQ1* G589D channels, once coexpressed with minK *in vitro*, feature smaller currents and result in a pronounced rightward shift in the voltage threshold of activation (13). In addition, the intronic *KCNQ1* IVS7-2A>G mutation that alters the splicing acceptor site and results in insertion of several amino acids to the C-terminal region of the protein, has been shown to lead to a complete loss-of-function defect (6). We have also demonstrated that the *KCNH2* R176W results in a reduced current density and slight acceleration in deactivation kinetics *in vitro* (24).

Even after excluding the 16 carriers of the *KCNH2* R176W mutation with moderate QT-prolonging effect, the prevalence estimate is 0.2% (95% CI 0.1%–0.3%). The prevalence estimate of 1/250 to 1/500 is striking and suggests that a considerable proportion of the Finnish population may be genetically predisposed to severe ventricular arrhythmias due to the four LQTS founder mutations. Despite the potency of these mutations to cause a disease phenotype, their penetrance is variable ranging from 21% to 34% (6,14) among clinical LQTS families. Moreover, the information on risk stratification is derived from LQTS patients and their relatives only, which precludes any definitive statements regarding the risk of life-threatening ventricular arrhythmias among the mutation carriers in the general population. Nevertheless, as the founder mutation carriers in the present survey have substantially longer QT intervals than non-carriers, it is evident that these individuals are at increased risk for arrhythmias if the repolarization reserve (32) is further challenged due to exposure to a QT-prolonging medication, hypokalaemia, or ischaemic or structural heart disease (33).

The findings and implications of the present study are not directly applicable to other populations where LQTS founder mutations do not exist or have not been detected until now. However, we feel that the present study stands as a forerunner to demonstrate that relatively prevalent genetic causes of markedly prolonged ventricular repolarization may indeed exist in the population. With the advent of constantly improving DNA sequencing techniques, this may also soon be explored in other populations. Early, presymptomatic identification of risk for ventricular arrhythmias, particularly upon exposure to certain medications, is of high priority since preventive measures can effectively avert sudden death (34). Even though in 75% of the cases the DNA analysis of the five most common LQTS genes confirms the LQTS diagnosis (35,36), prophylactic screening at the population level has not been practical due to the costs and rarity of the disorder. In Finland, targeted pre-prescription screening could become cost-effective in the future along with the rapidly evolving genetic screening measures. Especially in population isolates like Finland showing

enrichment of a limited number of variants, such screening could be exceptionally beneficial for the health care system.

We conclude that four LQTS mutations, *KCNQ1* G589D, *KCNQ1* IVS7-2A>G, *KCNH2* L552S, and *KCNH2* R176W, are surprisingly common in the Finnish population and seemingly represent founder mutations which have become enriched in this isolated population. These mutations lead to a considerable QT prolongation at the population level and could mark individuals at risk for arrhythmias even if clinical LQTS is not apparent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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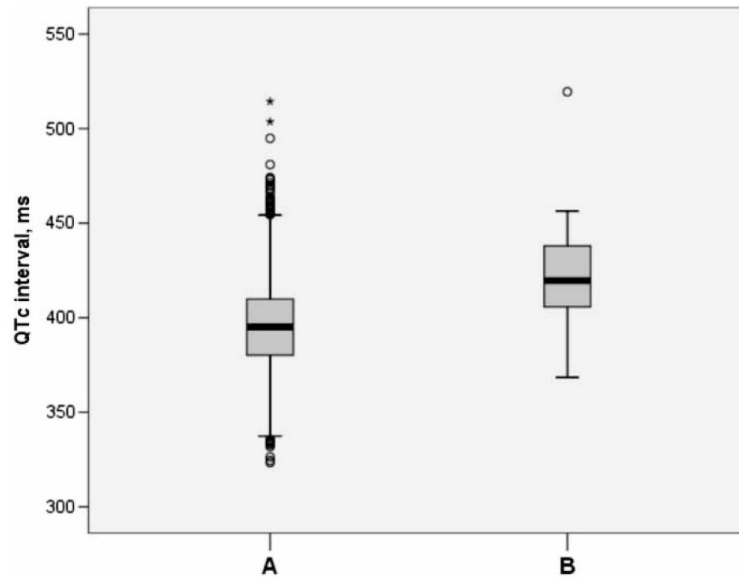
Figure 1.
The QTc intervals in founder mutation non-carriers (A) (n=4758) and carriers (B) (n=25) (P=1.26×10^{-9}), after exclusion of cases with potentially QTc-altering traits or medications. The boxes represent the median values (bolded horizontal lines) and the 25th to 75th percentiles of the mean QTc intervals. The fine lines refer to the highest and lowest values that are not outliers. Circles represent values >1.5-fold the interquartile range, and asterisks refer to values >3-fold the range indicated by the box.

Table I

The clinical characteristics of the founder mutation carriers (*n*=25) and non-carriers (*n*=4758) after exclusion of cases with potentially QTc-altering traits (bundle branch block, QRS ≥120 ms, atrial fibrillation or flutter, pacemaker) or medications.

	KCNQ1 G589D *n*=7	*KCNH2* L552S *n*=2	*KCNH2* R176W *n*=16	Non-carriers *n*=4758
Females/males	4/3	1/1	8/8	2524/2234
Age, years	43±7 (34–57)	38±2 (36–39)	53±11 (30–70)	51±14 (30–97)
Heart rate, bpm	55±5 (48–63)	60±16 (49–71)	61±7 (50–72)	63±11 (34–120)
QT interval, ms	451±33 (406–507)	442±32 (420–465)	414±33 (357–480)	388±30 (279–536) [a]
QTc interval, ms	435±40 (403–520)	438±26 (420–457)	430±20 (396–459)	396±22 (323–514) [b]

Data are presented as a mean±SD (range) unless otherwise indicated.

bpm=beats per minute; QTc=QT interval corrected for heart rate using Bazett's formula.

[a] P 2.17 × 10^{-10}

[b] P 1.26 × 10^{-9} in comparison of QT parameters among founder mutation carriers and non-carriers. Because of failures in genotyping for the individual mutations, the genotype numbers do not add up to the total of 5068 individuals.