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COMMON CANDIDATE GENE VARIANTS ARE ASSOCIATED WITH QT INTERVAL DURATION IN THE GENERAL POPULATION

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Abstract

Objectives—QT interval prolongation is associated with increased risk of sudden cardiac death at the population level. Because 30-40% of the QT-interval variability is heritable, we tested the association of common LQTS and *NOS1AP* gene variants with QT interval in a Finnish population-based sample.

Methods—We genotyped 12 common LQTS and *NOS1AP* genetic variants in Health 2000, an epidemiological sample of 5,043 Finnish individuals, using Sequenom MALDI-TOF mass spectrometry. ECG parameters were measured from digital 12-lead ECGs and QT intervals were adjusted for age, sex and heart rate with a nomogram (Nc) –method derived from the present study population.

Results—The *KCNE1* D85N minor allele (frequency 1.4%) was associated with a 10.5 ms (SE 1.6) or 0.57 SD prolongation of the adjusted QT_{Nc} interval ($p=3.6\times10^{-11}$) in sex-pooled analysis. In agreement with previous studies, we replicated the association with QT_{Nc} interval with minor alleles of *KCNH2* intronic SNP rs3807375 (1.6 ms (SE 0.4) or 0.08 SD, $p=4.7\times10^{-5}$), *KCNH2* K897T (−2.6 ms (SE 0.5) or −0.14 SD, $p=2.1\times10^{-7}$) and *NOSA1P* variants including rs2880058 (4.0 ms (SE 0.4) or 0.22 SD, $p=3.2\times10^{-24}$) under additive models.

Conclusions—We demonstrate that each additional copy of the *KCNE1* **D**85N **minor** allele is associated with a considerable 10.5 ms prolongation of the age-, sex- and heart rate-adjusted QT interval, and could thus modulate repolarization-related arrhythmia susceptibility at the population level. In addition, we robustly confirm the previous findings that three independent *KCNH2* and *NOSA1P* variants are associated with adjusted QT interval.

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Keywords

long-QT syndrome; QT interval; genetics; KCNE1; epidemiology

INTRODUCTION

Prolonged cardiac repolarization may associate with increased morbidity and mortality in the general population [1,2]. The distinctive feature in long QT syndrome (LQTS) is the prolongation of the QT interval on the surface ECG and high risk for ventricular tachyarrhythmias [3,4]. The underlying mechanisms involve mutations in ten genes coding for predominantly cardiac ion channels [5]. However, these disorders are collectively rare with a recent prevalence estimate of 1/2000 for LQTS [6] and therefore cannot account for the increased population risk of ventricular arrhythmias or sudden death.

Approximately 30-40% of the variation in QT interval duration is heritable [7-9]. Several epidemiological surveys have reported common ion channel polymorphisms to be associated with QT interval duration with varying levels of statistical support [10-13]. In addition, a genome-wide association study recently identified genetic variation at *NOS1AP* as a modulator of repolarization [14,15], not directly through ion channel function but perhaps by regulating intra-cardiac signaling. In the present survey, we assessed the effects of common LQTS gene variants and the recently characterized *NOS1AP* variants on QT interval duration utilizing a large, epidemiological cohort from the Finnish population.

METHODS

Study Population

The study population consisted of a two-stage stratified cluster sample of 8,028 individuals drawn from the Finnish Population Information System (http://www.vaestorekisterikeskus.fi/vrk/home.nsf/www/populationinformationsystem) for the Health 2000 survey. The material was collected between September 2000 and June 2001, and it is representative of the entire Finnish population of age ≥ 30 years [16]. DNA samples were collected from 6,334 individuals, and digital standard 12-lead ECGs were available from a total of 6,295 study participants. Clinical characteristics including medications, prior heart failure, history of myocardial infarction, prevalent diabetes and smoking status were determined as described previously [16]. Subjects with complete left or right bundle branch block (n=143), QRS duration ≥ 120 ms (n=205), atrial fibrillation/flutter (n=94), pacemaker (n=12), use of QT interval altering medication including digoxin (n=1064) or confirmed genetic diagnosis for one of four Finnish LQTS founder mutations [17] were excluded from the study population. A drug was considered to potentially prolong QT interval if it was listed in any of the four categories at the website www.qtdrugs.org (accessed November 2006). In addition, we excluded individuals taking any of the following additional agents that might affect the rate of ventricular repolarization: carbamazepine, flupentixol, levomepromazine, mefloquine, olanzapine, oxcarbazepine, periciazin, sertindole and trazodone. The final study population included 5,043 individuals. The study was performed according to the declarations of Helsinki and was approved by the Ethical Committees of the Hospital District of Helsinki and Uusimaa and the National Public Health Institute. A written informed consent was obtained from the participants.

Genetic Analyses

Eight nonsynonymous LQTS gene variants were selected for genotyping based on the following criteria: 1) the variant had been identified in the Finnish population based on our

previous studies on LQTS [17] and 2) the variant had evidence for a functional role in modifying cardiac repolarization in the literature (i.e. association with LQTS and/or QT interval duration or suggestive *in vitro* data). In addition, we assessed four recently described *NOS1AP* single nucleotide polymorphisms (SNPs) and an intronic *KCNH2* rs3807375 SNP that have been reported to be associated with QT interval duration in other population samples [12,15]. Genotyping was performed using Sequenom MALDI-TOF mass spectrometry (MassArray Compact Analyzer, Sequenom Inc, San Diego, CA, U.S.A.) and Applied Biosystems TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, U.S.A.) according to manufacturer's instructions (online Data Supplement Methods). All SNPs were tested for Hardy-Weinberg equilibrium with a chi-square test.

ECG measurements

A digital standard 12-lead ECG was recorded with Marquette MAC 5000 (GE Marquette Medical Systems, Milwaukee, WI, U.S.A.). The 12 leads were recorded simultaneously, and a digital median QRS-T complex was used for analyses. We used QT Guard software (GE Marquette Medical Systems, Milwaukee, WI, U.S.A.) to measure heart rate, and a custom-made software for all other measurements. The QT interval measurements were based on a previously described and validated algorithm [18]. The software calculates QT interval from QRS onset to T-wave offset, and a single observer (K.P.) reviewed measurements on-screen in a blinded fashion. For final analyses, we used the mean QT interval from all 12 leads. The intraobserver coefficient of variation was 0.7% for the mean QT interval in repeated ECG measurements in our recent study [19], and the same measurement methods were used also in the present survey. QT intervals were nomogram-corrected (Nc) for heart rate [20]. The correction equations were determined separately for each 10 beats per minute (bpm) heart rate range in the current study based on a previously described method [20]. In addition, the SNPs were tested for association with age-, sex- and RR interval- (heart rate) adjusted QT intervals. Left ventricular hypertrophy was considered to be present if Sokolow-Lyon voltage >35 mm[21] and/or gender-adjusted Cornell voltage-duration product >2440 mm·ms [22] was observed.

Statistical analyses

Histograms of all the variables were reviewed for normality. Using a stepwise linear regression model, we adjusted the mean QT_{Nc} intervals for age and sex [23,24] and determined the beta coefficient, 2-tailed p-value and partial R^2 for each covariate in the model. In addition, we tested additional covariates i.e. left ventricular hypertrophy, acute myocardial infarction, heart failure, prevalent diabetes, smoking, diuretics usage and geographical area for a possible explanatory role in the model. As these additional covariates accounted for less than 1% of the variation of QT_{Nc} interval in the study population, did not reach strong statistical significance ($p>0.001$) and in order to use a measure comparable to other studies, the QT_{Nc} residuals were derived from the age- and sex-adjusted model. The histograms of output residuals from the adjusted model were reviewed for normality (skewness 0.39, SE 0.03, kurtosis 1.10, SE 0.07). We tested for association using both a one-degree (1df) additive model and a two-degree freedom (2df) general test. In the 1df-test, we transformed the genotype to a continuous variable that corresponded to the number of minor alleles (0, 1, 2). Appropriateness of an additive genetic model was confirmed by evaluating the genotype-specific means for the QT_{Nc} residuals. In the 2df-test, the heterozygote and minor homozygote genotypes were converted to two dichotomous variables, with the major homozygote genotype as the reference. Nominal p-values are shown throughout the text without adjustment for multiple hypotheses. The Bonferroni-corrected [25] alpha level would be $p=5.0\times10^{-3}$ (0.05/10), considering the strongly correlated *NOS1AP* variants are counted as a single test. Hence the total number of independent tests is 10. The prevalence estimates with 95% confidence intervals were

derived from the weighted study population as described earlier [16]. Using four SNPs associated with QT interval duration, we constructed a QT-prolonging score composed of the sum of the predicted QT-prolonging effect of each genotype in milliseconds and tested for association of the genotype-score with QT_{Nc} on a continuous scale and in quintiles. The statistical analyses were performed in the SPSS 13.0/15.0 software (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 clinical characteristics of the study population are presented in Table 1. All selected SNPs were analyzed in the course of the study. Genotyping call rates ranged from 97.6 to 99.9% of the study sample, and all SNPs were in Hardy-Weinberg equilibrium ($p>0.01$). The genotype frequencies did not differ between males and females. The sex-pooled genotype-specific mean QT_{Nc} intervals are shown in Table 2. The results from the linear regression analysis of the age- and sex-adjusted mean QT_{Nc} are summarized in Table 3.

KCNE1 D85N (rs 1805128) minor allele was identifiable in 127 study participants in heterozygous form resulting in a prevalence estimate of 2.6% [95% CI 2.2-3.2] in the population, and three subjects were homozygous carriers of the allele. Each additional copy of the D85N minor allele was associated with a 10.5 ms higher adjusted QT interval (SE 1.6, $p=3.6-10^{-11}$). Accordingly, while the mean QT_{Nc} interval in subjects without this allele was 393 ± 20 ms (n=4684), the corresponding value in D85N heterozygotes was 404 ± 20 ms (n=127) and 415 ± 23 ms in homozygotes (n=3).

A 2.6 ms (SE 0.5, $p=2.1-10^{-7}$) shortening of the adjusted QT_{Nc} was observed per *KCNH2* K897T minor allele. The *KCNH2* intronic SNP rs3807375 was associated with a 1.6 ms (SE 0.4) increase of adjusted QT interval per minor allele QT_{Nc} ($p=4.7\times10^{-5}$). The SNP rs3807375 has previously been tested under a dominant model [12], and therefore we analyzed this intronic variant accordingly (effect size 2.3 ms, SE 0.6, $p=5.4\times10^{-5}$). The four *NOS1AP* variants were in strong LD (online Data Supplement Table 2) and resulted in statistically significant association with age- and sex-adjusted QT_{Nc} under an additive model of inheritance. The strongest association was observed for SNP rs2880058 with a 4.0 ms (SE 0.4) increase of adjusted QT interval per minor allele copy ($p=3.2\times10^{-24}$). The effect sizes and significance of each SNP on age-, sex- and RR interval-adjusted mean QT interval were similar to the age- and sex-adjusted mean QT_{Nc} (data not shown). Secondary analyses excluding all individuals older than 60 years, with QTc ≥ 500 ms, history of myocardial infarction and prevalent heart failure did not alter the results (data not shown). A secondary analysis excluding individuals with a history of myocardial infarction yielded equivalent results.

Using the genotype effect size for each of the four SNPs *KCNH2* rs3807375 and K897T, *KCNE1* D85N and *NOS1AP* rs2880058, we constructed a score ranging from 0 to 35.0 points based on the effect in milliseconds of each QT-prolonging genotype relative to the reference genotype. A score of 0 results for an individual who carries none of the genotypes associated with longer QT interval. A 1 point increase in the QT-prolonging score was associated with a 0.89 ms increase in the age- and sex-adjusted QT_{Nc} interval ($p=4.6\times10^{-38}$). For each quintile increase in the QT-prolonging score, the adjusted QT_{Nc} interval increased 2.4 ms ($p=1.6\times10^{-32}$). Accordingly, the mean QT_{Nc} in the first quintile was 388 ± 19 ms compared to a mean QT_{Nc} of 398 ± 20 ms in individuals in the fifth quintile ($p=8.3\times10^{-23}$). In addition, the odds ratio for a prolonged QT_{Nc} interval ($QT_{Nc}>419$

ms, the upper 90th percentile) was 1.11 [95% CI 1.08-1.13] per quintile increase in the QT-prolonging score ($p=1.5\times10^{-16}$).

DISCUSSION

Principal Findings

Using a large, epidemiological study cohort of more than 5,000 individuals of Finnish origin with well-characterized ECG phenotypes, we report association of three common LQTS gene variants in *KCNE1* and *KCNH2* and several correlated *NOS1AP* variants with QT interval duration.

KCNE1 D85N association

The most notable finding was the strong association of the *KCNE1* D85N variant [26], present in 2.6% of the population and resulting in a 10.5 ms age, sex- and nomogram-corrected QT-interval prolongation in heterozygous individuals. In a prior report by Gouas et al, this polymorphism in minK, the regulatory subunit of I_{Ks} channel, was examined in 200 subjects with the shortest and 200 with the longest QT interval from among 2,008 participants in a French community-based study [10]. Minor allele carriers had an increased odds of being in the longer QT group (p=0.03).

In studies based on clinical samples, the **D**85N has been identified in solitary patients with *torsade de pointes* in the absence of recognizable disease-causing mutations in other LQTS genes [27,28]. Wei et al studied 96 acquired LQTS patients and 46 subjects with normal QT intervals following anti-arrhythmic drug therapy [29]. *KCNE1* D85N appeared more prevalent in acquired LQTS subjects (7.3%) than in drug-tolerant patients (2.2%) [29]. Salisbury et al identified 11 carriers (11%) of **D**85N in a cohort of 98 LQTS-gene negative patients whereas 364 healthy controls had a significantly lower minor allele frequency with only nine heterozygous carriers (2.5%) [30]. A study by Westenskow et al reported *KCNE1* D85N in altogether thirteen carriers of LQTS-causing *KCNQ1* or *KCNH2* mutations who had evidence of a longer QTc compared to the non-carriers of the **D**85N **minor** allele [31]. *In vitro* electrophysiological studies have suggested a functional role of the D85N in reducing the I_{Ks} current under voltage clamp conditions [31,32].

Thus, in aggregate substantial evidence supports the role of the *KCNE1* D85N as a modifier of long QT syndrome and drug-induced *torsade de pointes*. Our finding of a striking effect of this SNP on baseline QT interval duration in a large unselected population supports the relevance of this variant to the general population. Ultimately, these findings may contribute to identification of patients with genetically determined reduced repolarization reserve[33,34] and increased risk of arrhythmias in general (LQTS) or upon exposure to QT-prolonging drugs.

KCNH2 (HERG) K897T and rs3807375 associations

We were the first group to report the common **K897T** substitution in the *KCNH2* gene and proposed a plausible mild phenotypic effect of this variant among female LQTS1 patients [35]. Upon studying 1,030 Caucasian men and women, Bezzina et al described longer QTc interval duration among carriers of the **K897T** major allele consistent with our earlier findings [36]. Gouas et al showed a higher frequency of the K897T minor alleles among 200 individuals with the shortest QTc intervals from 2,008 healthy French subjects [10]. Pfeufer et al reported a nearly 2 ms shortening of the QT interval per **K897T** minor allele copy in a population-based study of 3,966 individuals from southern Germany [13] similar to the most recent findings by Newton-Cheh et al [12]. Conflicting results exist in a study of randomly selected healthy Finnish individuals which observed QT prolongation among female carriers

of the minor allele [37]. Discrepant results have also been reported among the numerous *in vitro* electrophysiological experiments concerning the functional consequences of the *KCNH2* K897T polymorphisms [36,38-40]. In fact, the consequences of the K897T variant may differ in patients with varying degree of genetically modified I_{Kr} current [40]. Nevertheless, our present results confirm the majority of *in vivo* findings that the **K897T** minor allele is associated with moderate shortening of the QT interval under resting conditions.

In addition, we replicate the finding that an intronic *KCNH2* SNP (rs3807375) is associated with QT interval under an additive or dominant genetic model, as previously reported by Newton-Cheh et al [12]. This variant marks a pair of haplotypes at the locus, one of which was found to be associated with QT interval duration in the same direction in a study by Pfeufer et al [13]. The missense K897T and intronic rs3807375 show weak correlation (r^2=0.15) and thus likely represent independent signals.

NOS1AP variant association

In addition to the LQTS gene polymorphisms, we robustly confirmed the association of rs10494366 and three other *NOS1AP* SNPs in linkage disequilibrium, all of which showed association of minor alleles with longer QT interval ($p=8.3\times10^{-19}$ to 3.2×10^{-24}). The stronger statistical support up to five orders of magnitude suggests that SNPs other than rs10494366 are more strongly correlated to the as yet unrecognized causal variant. A genome-wide association study by Arking et al first reported the association of *NOS1AP* rs10494366 with modest but consistent QT prolongation [14], and subsequently these results have been replicated in a total of five published independent population-based samples until now [14,15,41]. The pathophysiological mechanisms mediating the *NOS1AP* effect on myocardial repolarization remain to be elucidated, but it is now evident that these SNPs, explaining up to 2% of the variation of QT interval in our model, do indeed modify myocardial repolarization.

SCN5A H558R variant possible association

SCN5A H558R [42] has been under intense investigation for a contribution to various arrhythmias including atrial fibrillation [43] and Brugada syndrome [44], but its role in myocardial repolarization has remained uncertain among community-based samples. Gouas et al reported modest association of the **H**558R **minor** allele with an increased odds of being in the longer QTc group in the D.E.S.I.R. study (p=0.01) [10]. Similarly, a study by Aydin et al demonstrated an association of **H558R** minor allele on QT interval prolongation in a twin cohort (p=0.025) [45]. We find modest replication of the association of the **H558R** minor allele with a 1.5 ms increase in age-, sex- and nomogram-corrected QT for each minor allele ($p=2.0\times10^{-3}$), but consider the existing evidence of association of this variant with QT interval duration to be inconclusive.

Other LQTS gene variants

KCNH2 R1047L [46] has been described to be associated with dofetilide-induced *torsade de pointes* [28,47], and leads to slower activation and inactivation kinetics *in vitro* [47]. According to our previous molecular genetic studies in LQTS patients, *SCN5A* A572D [48] and ***SCN5A* R190G [17]** appear to be slightly enriched among LQTS patients (6% vs. 4% controls for A572D **and 2% vs 0.6% controls for R190G)** [17]. *KCNE1* G38S [49] was reported to be associated with QT prolongation in men in a family-based study from Israel [50], but a study by Akyol et al in a German sample did not find a modifying effect of the **G**38S **minor** allele on QT interval duration [51], nor did the smaller study by Gouas et al [11]. The polymorphism *KCNE2* T8A has previously been reported to be associated with drug-induced *torsade de pointes* [27,52,53], but recently a study by Pfeufer et al found no

effect of this SNP on QT at the population level [13]. Based on our analyses in over 5,000 genotyped and phenotyped individuals, the *KCNH2* R1047L, *SCN5A* A572D, ***SCN5A* R190G,** *KCNE1* G38S and *KCNE2* T8A polymorphisms seem unlikely to modify the resting QT interval to a large extent in the Finnish population. It is unsettled, however, whether these variants account for alterations in QT interval in interaction with other genetic factors or with extrinsic stresses such as exercise, hypokalemia, ischemic or structural heart disease or **drug exposure** [54].

Potential clinical impact

Despite the marked significance levels in the current study, the allelic effect sizes remain relatively modest with the exception of *KCNE1* D85N. The R^2 values are all under 2.5% despite the noticeable prevalence of these common variants and reflect the relatively modest effects of these variants. Since QT interval prolongation is associated with increased mortality in patients with chronic [55] and acute [2] coronary artery disease and in men with cardiovascular disease [56] as well as in the general population [1,57], even subtle additive changes may reduce repolarization reserve and contribute to increased risk of arrhythmias. Furthermore, even small changes caused by common variants may become important at the population level. In the present survey, we constructed a genotype score of four validated QT-altering SNPs. The 10 ms difference in mean QT_{Nc} intervals among individuals with QT prolonging scores below the 20^{th} and greater than the 80^{th} percentiles of the QT genotype score is comparable to the QT prolonging effects of drugs withdrawn from the market [58] and thus potentially of clinical importance. Nevertheless, as about one third of the variation in QT interval duration is heritable [8], and the SNPs in the present study explain only a fraction of that, it is evident that other as yet unidentified heritable factors, independently or in interaction, must contribute to variability in cardiac repolarization.

Study Strengths and Limitations

The strength of the current study builds on the large, stratified cluster sample of over 5,000 individuals with surface ECGs and DNA that was designed to reflect the whole Finnish population of ≥ 30 years old. The collection of clinical data without regard to phenotype enabled assessment of potential confounding factors. Systematic evaluation of the ECG parameters by a single observer yielded precise ECG phenotypes. The correction for heart rate was based on the nomogram-method from the present study population thus allowing accurate adjustments. Furthermore, the availability of alternative methods for adjusting QT interval for heart rate (nomogram, RR-interval in a linear model) and the equivalence of results from them confirms the general relevance of the findings in the current study sample and in other populations that may use different QT adjusting methods. In order to detect more subtle effects, an even larger population sample would be required. This limitation applies particularly to the four SNPs that failed to demonstrate statistically significant effects on the evaluated QT parameters. Our study involved participants of Finnish origin only. Since the association studies on myocardial repolarization have thus far been restricted to the European ancestry, we cannot draw any definitive conclusions regarding the effects of these variants in populations of other ancestries.

CONCLUSIONS

In conclusion, we have demonstrated that the *KCNE1* D85N missense SNP is associated with a 10.5 ms prolongation of the age-, sex- and nomogram-adjusted QT interval. Despite the relative infrequency of the polymorphism, this variant stands as a plausible independent risk factor for repolarization-related arrhythmogenesis. In addition, we have convincingly replicated the association of the *KCNH2* intronic rs3807375 and missense K897T SNPs, and

several correlated *NOS1AP* variants in modulating the QT interval duration at the population level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical Characteristics of the Health 2000 Study Sample (n=5,043)

	Females	Males	Both
Number	2,691 (53)	2,352 (47)	5,043
Age, yr	52.4 ± 14.9 (30-97)	50.2 ± 13.1 (30-97)	51.4 ± 14.1 (30-97)
Heart rate, bpm	64.1 ± 10.4 (37-120)	62.3 ± 11.1 (34-113)	63.3 ± 10.7 (34-120)
Mean QT interval, ms	391.9 ± 29.6 (288-532)	384.7 ± 29.7 (279-536)	388.5 ± 30 (279-536)
Mean QT_{Nc} interval, ms	398.9 ± 18.7 (338-512)	387.6 ± 19.3 (323-514)	393.6 ± 19.8 (323-514)
Mean QTc interval, ms	401.9 ± 20.4 (333-504)	388.6 ± 22.1 (323-514)	395.7 ± 22.2 (323-514)
Left ventricular hypertrophy	418 (15.5)	459 (19.5)	877 (17.4)
Prevalent heart failure	31 (1.2)	8 (0.3)	39 (0.8)
History of myocardial infarction	35 (1.3)	77 (3.3)	112 (2.2)
Prevalent diabetes	82 (3.0)	105 (4.5)	187 (3.7)
Current smoking	457 (17.0)	670 (28.5)	1127 (22.3)
Diuretic usage	72 (2.7)	28 (1.2)	100 (2.0)

Values are presented as mean ± SD (range) for continuous variables, and as number of subjects (%) for categorical variables. Nc= nomogram–corrected for heart rate. QTc=QT interval corrected for heart rate according to the Bazett's formula [59]. Left ventricular hypertrophy assessed with Sokolow-Lyon voltage [21] and/or gender-adjusted Cornell voltage-duration product [22] criteria.

Table 2

Mean QT_{Nc} Intervals by Genotype for 12 Candidate Gene Single Nucleotide Polymorphisms

Gene	SNP	Amino acid change	Major homozygotes		Heterozygotes		Minor homozygotes	
			%	QT_{Nc}	%	QT_{Nc}	%	QT_{Nc}
KCNH2	rs3807375		32.4	392.2	49.4	393.9	18.2	394.8
KCNH2	rs1805123	K897T	67.9	394.3	28.8	392.0	3.3	389.8
KCNH2	rs36210421	R1047L	86.8	393.6	12.6	392.8	0.7	383.8
SCN5A		**R190G**	**99.1**	**391.9**	**0.9**	**393.6**	**0**	
SCN5A	rs1805124	H558R	64.0	392.9	32.0	394.3	4.0	396.9
SCN5A		A572D	93.8	393.5	6.1	393.4	0.1	400.0
KCNE1	rs1805128	D85N	97.3	393.2	2.6	403.7	0.1	414.6
KCNE1	rs1805127	G38S	34.4	393.1	49.0	393.7	16.6	393.9
KCNE2	rs2234916	T8A	99.0	393.5	1.0	392.9	0	
NOS1AP	rs2880058		42.3	390.5	45.5	395.0	12.2	398.2
NOS1AP	rs4657139		41.3	390.4	46.1	395.0	12.6	397.8
NOS1AP	rs10918594		43.8	390.7	44.0	395.1	12.3	398.0
NOS1AP	rs10494366		41.6	390.7	45.7	394.9	12.7	397.5

Percentages refer to prevalence estimates. SNP=single nucleotide polymorphism.

Table 3

Effect of SNPs on Age, Sex and Heart Rate (Nc) -Adjusted QT Interval in Health 2000

Gene	SNP	Genotypic Model				Allelic Model		
		Heterozygote	Minor homozygote	*P* 2 df	R^2	Per minor allele	*P* 1 df	R^2
KCNH2	rs3807375	2.1 (0.12)	2.9 (0.16)	1.4×10^{-4}	0.004	1.6 (0.08)	4.7×10^{-5}	0.004
KCNH2	K897T	−2.6 (−0.14)	−4.9 (−0.27)	1.4×10^{-6}	0.006	−2.6 (−0.14)	2.1×10^{-7}	0.006
KCNH2	R1047L	−0.5 (−0.03)	−10.8 (−0.58)	4.0×10^{-3}	0.002	−1.5 (−0.08)	4.9×10^{-2}	0.001
SCN5A	**R190G**	**−0.5(−0.03)**	-	$\mathbf{8.5\times10^{-1}}$	**0.000**	**−0.5(−0.03)**	$\mathbf{8.5\times10^{-1}}$	**0.000**
SCN5A	H558R	1.4 (0.08)	3.1 (0.17)	6.6×10^{-3}	0.002	1.5 (0.08)	2.0×10^{-3}	0.002
SCN5A	A572D	0.3 (0.02)	7.1 (0.39)	7.2×10^{-1}	0.000	0.5 (0.03)	6.6×10^{-1}	0.000
KCNE1	D85N	10.5 (0.57)	20.6 (1.12)	3.1×10^{-10}	0.009	10.5 (0.57)	3.6×10^{-11}	0.009
KCNE1	G38S	0.6 (0.03)	0.7 (0.04)	5.1×10^{-1}	0.000	0.4 (0.02)	2.9×10^{-1}	0.000
KCNE2	T8A	0.1 (0.01)	–	9.8×10^{-1}	0.000	0.1 (0.01)	9.8×10^{-1}	0.000
NOS1AP	rs2880058	4.5 (0.24)	7.7 (0.41)	2.3×10^{-23}	0.021	4.0 (0.22)	3.2×10^{-24}	0.021
NOS1AP	rs4657139	4.5 (0.24)	7.5 (0.41)	4.9×10^{-23}	0.022	4.0 (0.22)	9.0×10^{-24}	0.021
NOS1AP	rs10918594	3.9 (0.21)	6.5 (0.35)	2.2×10^{-22}	0.021	3.9 (0.21)	8.7×10^{-23}	0.020
NOS1AP	rs10494366	4.0 (0.22)	6.6 (0.36)	4.6×10^{-18}	0.016	3.5 (0.19)	8.3×10^{-19}	0.016

Values are differences from major homozygotes in milliseconds. Beta coefficients standardized to the SD of the age-, sex- and nomogram-adjusted residuals are shown in parentheses. Genotypic and allelic models refer to the genetic models described in detail in the Methods. **R2 = Proportion of variance explained**. The standard deviation of age-, sex- and nomogram-adjusted QT residuals is 18.39.