Common Genetic Variants, QT Interval, and Sudden Cardiac Death in a Finnish Population-Based Study

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Background—Although sudden cardiac death (SCD) is heritable, its genetic underpinnings are poorly characterized. The QT interval appears to have a graded relationship to SCD, and 35% to 45% of its variation is heritable. We examined the relationship among recently reported common genetic variants, QT interval, and SCD.

Methods and Results—We genotyped 15 common (minor allele frequency >1%) candidate single nucleotide polymorphisms (SNPs), based on association with the QT interval in prior studies, in individuals in 2 cohort studies (Health 2000, n=6597; Mini-Finland, n=801). After exclusions, we identified 116 incident SCDs from the remaining sample (n=6808). We constructed a QT genotype score (QTscore) using the allele copy number and previously reported effect estimates for each SNP. Cox proportional hazards models adjusting for age, sex, and geographical area were used for time to SCD analyses. The QTscore was a continuous independent predictor of the heart rate–corrected QT interval (P<10^-10). Comparing the top with the bottom quintile of QTscore, there was a 15.6-ms higher group mean QT interval (P<10^-8). A 10-ms increase in the observed QT interval was associated with an increased risk of SCD (hazard ratio, 1.19; 95% confidence interval, 1.07 to 1.32; P=0.002). There was no linear relationship between QTscore and SCD risk; although in post hoc secondary analysis there was increased risk in the top compared with the middle QTscore quintile (hazard ratio, 1.92; 95% confidence interval, 1.05 to 3.58; P=0.04).

Conclusions—Our study strongly replicates the relationship between common genetic variants and the QT interval and confirms the relationship between the QT interval and SCD but does not show evidence for a linear relationship between QTscore and SCD risk. (Circ Cardiovasc Genet. 2011;4:305-311.)

Key Words: death, sudden genetics QT interval electrocardiography mortality electrophysiology

Sudden cardiac death (SCD) is a leading cause of mortality worldwide. Rare genetic syndromes are well described, but their contribution to total burden of SCD is low, accounting for fewer than 5% of deaths. There is interest in understanding the role of common genetic variants in SCD risk, but, to date, reproducible examples have been difficult to identify. Common variants are expected to confer only a small increase in SCD risk individually because they would otherwise be subject to strong negative selection. As a complement to primary genetic discovery in SCD samples, we hypothesized that common variants that are associated with SCD risk factors may influence the risk of SCD. Consistent with this hypothesis are recent observations that common variants associated with electrocardiographic QT interval or with myocardial infarction (MI) are also associated with SCD.

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Prolongation of the QT interval is associated with increasing risk of SCD, and 35% to 45% of its variation can be attributed to additive genetic factors, therefore offering a tractable intermediate phenotype for the study of SCD genetics. Through large multicenter genome-wide association studies, we and other investigators have identified several common variants that affect interindividual variability in QT...
interval duration.\textsuperscript{11,13} Although individual common variants would be expected to result in only modest increments in SCD risk, these common variants could, in aggregate, increase SCD through influencing susceptibility to arrhythmogenic triggers such as myocardial ischemia, electrolyte disturbances, or QT-prolonging medications.

In this study, we studied a large, population-based cohort in Finland: (1) to attempt to replicate the association of these common genetic variants with QT interval, (2) to confirm the relationship between QT interval and SCD, and (3) to explore the association between a score reflecting the joint influence of the variants and the risk of SCD.

Methods

Study Population

The Health 2000 Study population is a cross-sectional cohort drawn from the Finnish Population Information System (http://www.vaestorekisterikeskus.fi/). The survey was carried out in Finland in 2000 to 2001. The implementation of the survey is described in detail elsewhere (http://www.tervey2000.fi/doc/methodologyrep.pdf).\textsuperscript{14} The study involved a 2-stage, stratified cluster sample representative of the whole adult Finnish population age \textgeq\ 30 years. The Health 2000 sample comprised 8028 individuals, of whom 79.6\% (6354 individuals; 2876 men and 3478 women) participated in a comprehensive health examination including questionnaires, measurements (eg, blood pressure, resting ECG), and physician’s physical examination. DNA samples were collected from 6597 subjects and digital ECGs were available from 6295 subjects.

The Mini-Finland Health Survey was carried out from 1978 to 1980.\textsuperscript{15} The study involved a 2-stage, stratified cluster sample representing the whole Finnish population aged 30 years or over. The sample size was 8000 individuals. Of the original sample, 1286 individuals living in 7 cities (Helsinki, Kuopio, Lahti, Oulu, Salo, Tampere, and Turku) were invited to a health reexamination in 2001, and 985 (77\%) participated in the follow-up study. DNA samples were available from 801 subjects of the Mini-Finland Health Survey.

Subjects \textgeq\ 80 years old at baseline in either the Health 2000 or Mini-Finland study were excluded from the current investigation. For analysis of the association of the QT score with the observed QT interval, subjects were excluded if QT interval was not available, if the study ECG showed atrial fibrillation (n=55), QRS \textgeq\ 120 ms (n=148), or if the subject was using QT-prolonging (n=1692) or QT-shortening (digoxin, n=90) medications. Subjects taking QT-altering medications were not excluded from analyses of the association of the QT score with SCD. A drug was considered to potentially prolong the QT interval if it was listed in any of the 4 categories in the list maintained at http://www.qtdrugs.org. Digoxin was classified as the sole QT-shortening medication. Mini-Finland participants were not included in analyses of QT interval because ECG intervals had not been measured.

Study Samples and Data Sources

Follow-up data were obtained using national active surveillance and health care registers in Finland. The National Causes-of-Death register (maintained by Statistics Finland) includes data on the underlying and immediate cause of death as well as up to 2 contributing causes of death for all deaths in Finland. The Finnish Hospital Discharge Register, maintained by the National Institute for Health and Welfare, includes date of admission, date of discharge, and diagnoses associated with admission. The National Drug Reimbursement Register, maintained by the National Institute for Health and Welfare, includes date of admission, date of discharge, and diagnoses associated with admission. The National Causes-of-Death register, the Finnish Hospital Discharge Register that includes date of admission, date of discharge, and diagnosis associated with admission, and the National Drug Reimbursement Register. When the primary reviewers disagreed on the cause of death, cases were reviewed by 2 additional independent physicians, and a final adjudication was achieved by consensus. In total, 490 deaths were adjudicated. There was agreement in 439 of 495 (90\%) cases, and the remaining 51 cases were adjudicated with 2 additional reviewers. Adjudication of cause of death was blinded to genotyping data.

Deaths were adjudicated as probable SCD, possible SCD, unlikely SCD, and unknown cause of death. Eligible deaths for adjudication included out-of-hospital deaths and deaths within 10 days of hospitalization. Probable SCD was defined as a death in which a cardiac cause was listed as the immediate or underlying cause of death and death was not known to be unrelated to arrhythmia. Possible SCD was defined as a death in which the immediate or underlying cause of death was noncardiac, but cardiac disease was present and could reasonably have contributed to arrhythmia based on mechanism (eg, unexpected death due to aspiration in a patient with a prior MI), or death that could have been arrhythmic based on circumstance (eg, death of a driver in a motor vehicle crash, death while swimming). Unlikely arrhythmic cause was defined as death from an explained medical cause unrelated to cardiac disease (eg, cancer death, massive blood loss, sepsis, pulmonary embolism, stroke) or from a cardiac cause that was known to be nonsudden or unrelated to lethal arrhythmia (eg, death due to myocardial rupture after MI, death caused by endocarditis). Unknown cause of death included deaths for which insufficient data were available. We excluded deaths in individuals who had been hospitalized for more than 10 days before death. After exclusions, in total there were 84 probable sudden cardiac deaths, 32 possible sudden cardiac deaths, 347 unlikely sudden cardiac deaths, and 30 unknown etiology deaths. Probable and possible sudden cardiac deaths were pooled in the SCD analyses. Autopsies were performed in 38.9\% of all deaths, 62.6\% of SCDs, and 73.0\% of out-of-hospital SCDs. The median observational time was 8.1 years for Health 2000 and 7.8 years for Mini-Finland health.

Prevalent coronary heart disease (CHD) was defined as one of the following: (a) physician diagnosis during the survey health examination of previous MI or coronary disease requiring surgical or percutaneous revascularization; (b) previous hospital discharge with a diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21-I22); (c) pathological Q-waves or Minnesota code 1.1, or 1.2 together with 5.1 to 2 in the ECG; or (d) history of coronary revascularization procedure in the hospital discharge records.

QT Interval

The QT interval was measured from 12-lead digital ECGs (recorded with Marquette MAC 5000, GE Marquette Medical Systems, Milwaukee, WI) using a validated automated algorithm.\textsuperscript{16} As previously reported,\textsuperscript{17} the QT interval from QRS onset to T-wave end was measured in each lead from the median QRS-T complex, which is a digitally averaged complex from the full 10-second recording and is automatically produced for each lead by the software (QT Guard, GE Marquette Medical Systems). In this study, the QT interval was defined as the mean of these 12 measurements. The QT intervals were corrected for heart rate using a validated nomogram-correction (QT\textsubscript{NC}) method.\textsuperscript{18} The nomogram-corrected QT interval=measured QT interval\times(394.04 ms\div(\text{heart rate}+b)), where “a” and “b” were determined separately for each 10 beats per minute heart rate range. Example: for heart rate 60 to 68 “a”=−2.18 and “b”=525.01 ms, for heart rate 69 to 78 “a”=−1.67 and “b”=489.94 ms (see online-only Data Supplement Table).
Genotyping
A total of 15 independent SNPs were reported in 2 genome-wide association studies\(^{11,13}\) to have genome-wide significant association with QT duration \((P<5 \times 10^{-8})\). Multiple SNPs at a given locus were included only if they were in low linkage disequilibrium with each other. Because the primary NOS1AP SNP is known to have a very strong effect and there is extensive linkage disequilibrium across the region, we only included the top SNP at NOS1AP. Genotyping of genomic DNA was performed using the Sequenom iPLEX Gold assay (MALDI-TOF mass spectrometry, MassARRAY Analyzer Compact, Sequenom Inc. San Diego, CA) according to the manufacturer’s instructions. Assays were designed using MassARRAY Assay Design 3.1 software. Sex markers were included in the iPLEX design for detection of plate swaps. Genotypes were automatically assigned and manually confirmed using MassARRAY TyperAnalyzer 4.0 software. Passing SNPs were required to have at least 80% assigned and manually confirmed using MassARRAY TyperAnalyzer 4.0 software. Passing SNPs were required to have at least 80% genotyping success and Hardy-Weinberg equilibrium, \(P>0.0001\); 1 SNP failed. Individuals with successful genotype calls for fewer than 8 of 14 SNPs were excluded from analyses.

Statistical Analysis
Three primary analyses were performed: (1) association between the QT genotype score \((QT_{score}\) see definition below) and the QT\(_{NC}\) (2) observed QT\(_{NC}\) as a predictor of SCD, and (3) QT\(_{score}\) as a predictor of SCD. A QT genotype score \((QT_{score}\) was constructed using the allele copy number and the previously established\(^{13}\) effect estimates for the 14 SNPs using the following formula: \(QT_{score}=\text{[SNP1 allele copy number]} \times \text{(SNP1 effect estimate in predicted ms)} + \text{[SNP2 allele copy number]} \times \text{(SNP2 effect estimate in predicted ms)} + \ldots \) through SNP14. SNP genotypes that were missing were imputed to have allele copy number equal to 2 times the coded allele frequency through SNP14. QT genotype scores that were missing were imputed to have allele copy number equal to 2 times the coded allele frequency in the total sample. The genotype score was expressed in “predicted ms” of expected change in the QT interval.

All analyses included adjustment for age, sex, and geographic region. In analyses of SCD risk, additional adjustments were performed for use of QT-altering medications and prevalent CHD. To determine the referent quintile in these analyses, we first plotted the QT\(_{NC}\) or QT\(_{score}\) against SCD by decile (11 equal groups) to determine whether a nonlinear U- or J-shaped relationship existed. Multivariable linear regression models were used for cross-sectional association of genotype or QT\(_{score}\) with QT\(_{NC}\) and Cox proportional hazards models for association with time to SCD. Age was accounted for in the time scale of the Cox proportional hazards models for all SCD analyses. For single SNP to QT interval analyses, the threshold for significance was set at \(P<0.007\) (0.05/14×2 for a 1-sided test of association in the same direction as the original report). For other primary analyses, significance was defined as 2-sided \(P<0.05\); secondary analyses were exploratory.

Results
Demographic and clinical descriptive data for the total sample and SCD cases for Health 2000 and Mini-Finland are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics of Study Participants and SCD Cases in the Health 2000 and Mini-Finland Surveys</th>
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<td>QT_{NC}, ms, mean±SD</td>
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\(\star\)Dyslipidemia defined as LDL cholesterol >3.0 mmol/L, triglycerides >2.0 mmol/L, or HDL cholesterol <1.0 mmol/L in men or HDL cholesterol <1.2 mmol/L in women.

Table 1. Demographic and Clinical Characteristics of Study Participants and SCD Cases in the Health 2000 and Mini-Finland Surveys

QT SNP Association With QT Interval
All SNPs but one (SNP rs17779747) were independently associated with QT interval in the same direction as in the QTGEN or QTSCD studies \((P<0.007\); Table 2). The correlation of effect estimates in Health2000 to the original QTGEN and QTSCD effect sizes was 0.99. The QT\(_{score}\) weighted by the effect size observed in QTGEN and QTSCD was a continuous independent predictor of QT\(_{NC}\) in a linear regression model after adjustment for age, sex, and geographic study region \((P<10^{-107};\) Figure 1). The mean QT\(_{NC}\) in the top quintile was 15.6 ms higher than the bottom quintile \((P<10^{-84})\). The QT\(_{score}\) explained 8.6% of variation in QT\(_{NC}\), after adjustment for age, sex, and geographic study region.

QT Interval as a Risk Factor for SCD
A 10-ms increase in QT\(_{NC}\) was associated with an increased risk of possible or probable SCD in a Cox proportional hazards model after adjustment for sex and geographic study region \((HR, 1.19; 95\% \text{ confidence interval } [CI], 1.07 \text{ to } 1.32; P=0.002)\) and after additional adjustment for prevalent CHD and QT-altering medication use \((HR, 1.07; 95\% \text{ CI, } 1.054 \text{ to } 1.30; P=0.003)\). The relationship between QT\(_{NC}\) and SCD appeared to be roughly linear across the range of QT\(_{NC}\) quintiles (Figure 2). Results were unchanged using age- and sex-adjusted residuals (data not shown).

SCD risk was also assessed using a dichotomous previously reported threshold for QT prolongation \((QT_{NC}>450 \text{ ms for men or } >470 \text{ ms for women})^9\). The risk of SCD was 1.3% below and 24% above this threshold \((HR, 13.3; 95\% \text{ CI, } 4.7 \text{ to } 37.7; P=1 \times 10^{-6}, \text{ after adjustment for sex and geographic region; } HR, 12.7; 95\% \text{ CI, } 4.2 \text{ to } 38.6; P=7 \times 10^{-6} \text{ after additional adjustment for prevalent CHD and QT-altering drugs})\). Significance testing using Fisher exact test without covariate adjustment was similar \((P=6 \times 10^{-5})\).

QT\(_{score}\) and Risk for SCD
None of the SNPs that contributed to the QT\(_{score}\) were associated with SCD risk, when considered individually (Table 2). The continuous QT\(_{score}\) as a predictor of possible or probable SCD showed a nonsignificant increase in SCD risk for increasing QT\(_{score}\) \((HR, 1.30 \text{ per } 10 \text{ predicted millisecond increase in } QT_{score}; 95\% \text{ CI, } 0.87 \text{ to } 1.94; P=0.20, \text{ after adjustment for sex and geographic region})\). Conditioning on identical exclusion
criteria applied to the QTNC to SCD analyses (ECG unavailable, >80 years old, presence of pacemaker, left bundle-branch block, right bundle-branch block, QRS >120, use of QT-prolonging drug, use of digoxin) did not change the finding.

In secondary post hoc analyses, the QTscore plotted against SCD by QTscore quintile suggested a U-shaped relationship (Figure 3) so the middle quintile was considered as the referent category. The risk of SCD was higher in the top QTscore quintile compared with the middle quintile (HR, 1.92; 95% CI, 1.05 to 3.58; \(P = 0.04\) with adjustment for sex and geographic region; and HR, 1.90; 95% CI, 1.02 to 3.55; \(P = 0.04\) with additional adjustment for CHD and QT-altering drugs).

Discussion

We strongly replicated the association between several recently identified common genetic variants and the QT interval, individually and in aggregate. We confirmed the relationship between the QT interval and SCD. There was no evidence for a linear relationship between QTscore and SCD risk. In post hoc analysis, there appeared to be increased SCD risk at fourth and fifth QTscore quintiles compared with the median quintile. More generally, our findings support the strategy of studying common variants that contribute to a dichotomous trait by harnessing the relationship between common variants and an

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<th>HWE p</th>
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Chr indicates chromosome; Pos, genome position; Cod. freq., coded allele frequency; and HWE, Hardy-Weinberg equilibrium.

SNP effects are represented as the change in QT (in ms) per copy of the coded allele (for SNP versus QTNC), selected based on a positive QT interval effect in the QTGEN or QTSCD publications, and HR for SCD per copy of the coded allele (for SNP versus SCD). Values represent the additive effect of each coded allele.

*SNP positions are shown in reference to National Center for Biotechnology Information reference sequence 36.
†Call rates are shown for each individual SNP after exclusion of individuals with <80% genotyping success for each genotyping pool separately.
‡HR estimated using Cox proportional hazards model with age as the time scale.

Figure 1. Observed difference in QTNC by QTscore quintile (n=1103 per quintile) in comparison to the lowest quintile (Q1) and the predicted difference in QTNC. Error bars represent 95% CIs. Note, QTscore quintile includes exclusion for unavailable ECGs (ECG needed for QTNC calculation).

Figure 2. A graded relationship was observed between QTNC quintile (n=1175 subjects per quintile) and HR for SCD after adjustment for sex, geographic region, prevalent CHD, and use of QT-altering medications. Error bars represent the 95% CIs of the HR for SCD.
intermediate phenotype. It is well established that the rare mendelian diseases of extreme QT duration, the long-QT syndrome and short-QT syndrome are risk factors for SCD, but this is the first illustration that multiple common variants that contribute to repolarization, together, may affect risk of SCD in the general population. Of note, none of the individual SNPs that constitute the score were independently associated with SCD, so they would not have been detectable in primary analyses based on association with SCD risk.

In the present study, the QT genotype score was highly associated with the observed QT interval, strongly replicating the findings of the QTGEN and QTSCD studies. In the QTGEN study, the top quintile of QT genotype score was associated with an approximately 9 to 12 ms higher QTc compared with the median quintile. The comparatively weak QT effect, but this would need to be tested in an independent sample.

How might a QT genotype score offer additional risk prediction to the observed QT? Rather than simply reflecting the repolarization time, the QTscore may be a measure of susceptibility to arrhythmogenic stimuli. Uniform repolarization is maintained by multiple redundant mechanisms, a concept termed “repolarization reserve.” A single defect in one of these redundant pathways may reduce repolarization reserve but remain subclinical (and not reflected in the measured QT interval) until a “second hit” such as a drug exposure or myocardial ischemia unmasks the defect and provides the substrate for fatal arrhythmia. Indeed, many SCD cases in our study occurred on a background of risk factors for myocardial ischemia. The QTscore also may represent a subject’s lifelong exposure to genetically determined QT prolongation and may be more strongly associated with SCD than the QT interval measured in the resting, unperurbed state at one point in time.

Common variants in NOS1AP have been previously reported to be associated with the QT interval in individuals with congenital long-QT syndrome and more recently with SCD in unselected populations. Specifically, 2 independent signals have been associated with SCD: rs16847548, which is also associated with the QT interval, and rs12567209, which is associated with SCD only. The NOS1AP variant in our study (rs12143842) is correlated to rs16847548 (r²=0.818) but not to rs12567209 (r²=0.027). Though the NOS1AP SNP in our study did not reach statistical significance for association with SCD on its own (HR, 1.31; P=0.06), it has previously been shown to be associated with SCD with nearly identical HRs of 1.26 to 1.33. Of note, in prior studies, adjustment for QT interval attenuated but did not eliminate the association between rs16847548 and SCD, indicating that at least some of the effect of the rs16847548 (or its proxies) is mediated through its QT-prolonging effect.

Aside from these NOS1AP variants, relatively few common variants that contribute to SCD risk have been identified. Common SCD variants may be difficult to identify because SCD is a heterogeneous phenotype, representing the downstream end product of diverse underlying causes, case adjudication is challenging and often retrospective, and studies are underpowered because of the challenge of enrolling large SCD cohorts. The use of intermediate phenotypes can prove fruitful, as demonstrated by the relationship of common variants to low-density lipoprotein, which are also generally related to MI.

The methodologic advantages of this study are its use of large, population-based cohorts, prospective ascertainment of clinical data, a high rate of autopsies among SCD cases, and complete follow-up. The major limitations of this study are its low power to detect individual SNP effects due to small sample size,
possible survivor bias resulting from the older age at time of DNA collection in the Mini-Finland study, and imprecision in the case adjudication for SCD that relied on administrative data sources. Misclassification of noncardiac deaths as SCD could bias toward the null hypothesis of finding no association. Additionally, the SCD definition employment relies heavily on the presence of concomitant heart disease and thus may underestimate primary arrhythmic sudden deaths, a group in whom genetic causes are potentially more important. Last, not all QT prolongation is associated with increased SCD, such as that associated with amiodarone or ranolazine use. Analogously, it is possible that some variants that alter repolarization are arrhythmogenic while others are not.

In conclusion, our study strongly replicates the association between common genetic variants and the QT interval and suggests a relationship between these variants in aggregate and SCD. As additional QT interval variants are identified, these may add additional prognostic information to such genotype scores.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

There are more than 300,000 sudden cardiac deaths (SCD) annually in the United States. Although there are known genetic syndromes that account for high sudden death risk in individuals, these account for only a small proportion of all sudden deaths. The current study sought to identify common genetic variants that contribute to SCD risk in the general population. The authors created a list of candidate variants that are known to be associated with electrocardiographic QT interval (an intermediate phenotype for SCD) and calculated a QT genotype score, based on the QT interval effect per allele copy number, summed over all variants. They validated the robust association between these variants in aggregate and the continuous QT interval (an intermediate phenotype for SCD) and calculated a QT genotype score, based on the QT interval effect per allele copy number. There was no evidence, however, for a linear relationship between the QT genotype score and SCD risk.
Common Genetic Variants, QT Interval, and Sudden Cardiac Death in a Finnish Population-Based Study

Peter A. Noseworthy, Aki S. Havulinna, Kimmo Porthan, Annukka M. Lahtinen, Antti Jula, Pekka J. Karhunen, Markus Perola, Lasse Oikarinen, Kimmo K. Kontula, Veikko Salomaa and Christopher Newton-Cheh

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SUPPLEMENTAL MATERIAL

Supplementary table 1. Nomogram-corrected QT interval

Nomogram-corrected QT interval = measured QT interval + correction value

correction value (ms) = 394.039219191961 – (a × heart rate + b)

<table>
<thead>
<tr>
<th>Heart rate (beats per minute)</th>
<th>a</th>
<th>b</th>
</tr>
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<tr>
<td>&lt;50</td>
<td>-2.92</td>
<td>564.69</td>
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<tr>
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