Published in final edited form as:

Heart Rhythm. 2012 July ; 9(7): 1099–1103. doi:10.1016/j.hrthm.2012.02.019.

A COMMON VARIANT NEAR *KCNJ2* GENE IS ASSOCIATED WITH T-PEAK TO T-END INTERVAL

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Abstract

Background—T-peak to T-end (TPE) interval on the electrocardiogram (ECG) is a measure of myocardial dispersion of repolarization and is associated with increased risk of ventricular arrhythmias. The genetic factors affecting the TPE interval are largely unknown.

Objective—We sought to identify common genetic variants that affect the TPE-interval duration in the general population.

Methods—We performed a genome-wide association study on 1 870 individuals of Finnish origin participating in the Health 2000 Study. TPE interval was measured from T-peak to T-wave end in leads II, V2 and V5 on resting ECGs and the mean of these TPE intervals was adjusted for age, sex and Cornell voltage-duration product. We sought replication for a genome-wide significant result in the 3 745 subjects from the Framingham Heart Study.

Results—We identified a locus on 17q24 that was associated with the TPE interval. The minor allele of the common variant rs7219669 was associated with a 1.8-ms shortening of the TPE

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CONFLICTS OF INTEREST: None

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interval ($P=1.1\times 10^{-10}$). The association was replicated in the Framingham Heart Study (-1.5 ms, $P=1.3\times 10^{-4}$). The overall effect estimate of rs7219669 in the two studies was -1.7 ms ($P=5.7\times 10^{-14}$). The common variant rs7219669 maps downstream of *KCNJ2* gene, in which rare mutations cause congenital Long- and Short-QT syndromes.

Conclusion—The common variant rs7219669 is associated with the TPE interval and is thus a candidate to modify repolarization-related arrhythmia susceptibility in individuals carrying the major allele of this polymorphism.

Keywords

Electrocardiography; Repolarization; T wave; Epidemiology; Genetics; Polymorphism

INTRODUCTION

The interval from the peak of the T wave to the end of the T wave (T-peak to T-end interval, TPE) on the electrocardiogram (ECG) is a measure of myocardial dispersion of repolarization. Increasing evidence suggests that TPE interval may predict arrhythmia susceptibility in patients with various cardiovascular diseases.¹⁻⁴ Recently, prolongation of the TPE interval has been reported to be associated with sudden cardiac death in a community-based study.⁵

A Danish Twin study reported a heritability estimate of 46% of the TPE interval with evidence for an additive genetic effect.⁶ However, the genetic factors influencing the duration of the TPE interval are largely unknown. A few gene variants, initially associated with QT-interval duration, have been shown to affect TPE interval,^{7, 8} but these polymorphisms explain only a fraction of the heritability of the trait. In the present study, we sought to identify novel gene variants that affect the TPE interval using a genome-wide association (GWA) analysis and replication in independent study populations with well-characterized ECG phenotypes.

METHODS

Study populations

The Health 2000 Study was a two-stage stratified cluster sample of 8 028 Finnish adults aged 30 years. The survey included comprehensive health interviews, physicians' clinical examinations, digital standard 12-lead ECG recordings from 6 295 participants and DNA samples from 6 334 individuals.⁹ The genome-wide analysis was carried out in a subset of 2 212 original Health 2000 Study participants with metabolic syndrome or their matched controls. After quality-control procedures, 2 138 genotyped individuals were available for the study. Subjects carrying Finnish LQTS founder mutations ($n=27$),¹⁰ or having ECGs with Minnesota coding for Wolff-Parkinson-White pattern ($n=1$), paced rhythm ($n=12$), atrial fibrillation ($n=90$), atrial flutter ($n=1$), complete left bundle branch block ($n=60$) or complete right bundle branch block ($n=69$), or using of QTprolonging drugs (First category on Drugs with risk of *torsade de pointes*) ($n=129$) were excluded.⁷ The final study population consisted of 1 870 individuals. The replication sample included 3 745 participants from the 3rd generation of the Framingham Heart Study (FHS)¹¹ meeting the same criteria. Both studies were performed according to the declaration of Helsinki and were approved by the respective Ethical Committees. A written informed consent was obtained from all participants.

ECG measurements

In Health 2000 and Framingham Heart Study, standard 12-lead resting ECGs were recorded using Marquette MAC 5000 ECG recorder (GE Marquette Medical Systems, Milwaukee, WI, USA). In Health 2000, as previously described,⁷ TPE intervals were measured from digital ECGs using a custom-made software and a previously validated algorithm.¹² The software measured QT and TPE interval in each lead from a median QRS-T complex, which in each lead represents a digitally averaged complex from the full ten-second ECG recording. A single observer (K.P.) reviewed the measurements in a blinded fashion. In the Framingham Heart Study, TPE intervals were calculated by subtracting QTpeak (interval from QRS onset to peak of T wave) from the QT interval (interval from QRS onset to T-wave offset) as measured using digital calipers on scanned ECGs. TPE-interval measurements were available in leads II, V2, and V5 in both study populations. The mean of TPE interval in these leads was used in the analyses, which may optimize the precision of the measure. TPE intervals were neither corrected for heart rate nor for QT interval.¹³

Genome-wide analysis

Samples from the Health 2000 Study cohort were genotyped using the Illumina Infinium HD Human 610-Quad BeadChip (Illumina, Inc., San Diego, CA, USA). Probe signals were clustered into genotype groups using the Illuminus algorithm⁹ and subsequent quality criteria for single nucleotide polymorphisms (SNP) inclusion were as follows; a call rate 95%, minor allele frequency 2%, and a HWE P-value 1×10^{-4} . Subsequently, 52 645 SNPs of the 598 203 genotyped SNPs were excluded. Sample QC additionally excluded 35 samples that had high relatedness ($\pi > 0.2$). All samples had a genotyping success rate $> 95\%$. After these quality-control procedures, 550 284 SNPs and 2 138 genotyped individuals were available for the study. We imputed SNP genotype data using MACH 1.0.16 with the HapMap3 CEU and TSI populations as a reference, which was further extended with a population specific sample set of 81 Finns (imputation methods and reference samples previously described by Surakka et al.¹⁴). A total of 1 257 079 autosomal SNPs were available for analysis after quality control, of these, 541 864 SNPs were directly genotyped.

Statistical methods

Using linear regression analysis, we adjusted the mean TPE interval calculated from leads II, V2 and V5 for age, sex and Cornell voltage-duration product [mm-ms, male: $(RaVL + SV3) \times QRS$, female: $(RaVL + SV3 + 8) \times QRS$], all of which were statistically significant covariates ($P < 0.05$). Cornell voltage-duration product is a measure of left ventricular hypertrophy that has been shown to be associated with electrocardiographic repolarization parameters including TPE interval.¹⁵⁻¹⁹ Other non-significant covariates that were not included in the final model were current smoking status, hypertension, coronary artery disease, previous myocardial infarction, heart failure, and diabetes mellitus. Statistical analysis was carried out using the SPSS software 17.0 (SPSS, Inc., Chicago, IL, USA) and PLINK V1.06 (<http://pngu.mgh.harvard.edu/purcell/plink/>). FHS analyses were conducted using the lme4 package in R. A threshold P-value of 5.0×10^{-8} was applied for genome-wide significance.

RESULTS

The Health 2000 GWA analysis of the T-peak to T-end interval

The clinical characteristics of the Health 2000 Study population are shown in Table 1. Of the 1 870 study subjects, 902 (48 %) were men. The mean age was 50.4 ± 10.9 years and the mean QT interval and QTc interval (Bazett) were 388.9 ± 29.7 ms and 395.3 ± 22.4 ms, respectively. The mean TPE interval was 73.6 ± 8.4 ms.

In the Health 2000 cohort, we observed the strongest association in the genome for rs7219669 (MAF 0.38) on chromosome 17q24 with a 1.8-ms shortening of the TPE interval per minor allele T copy ($P=1.1\times 10^{-10}$) (Figure 1, Table 2). In addition, we identified a suggestive association of rs17749681 (MAF 0.38) at chromosome 16p13 with a 1.4-ms prolongation of the TPE interval ($P=2.1\times 10^{-7}$).

Replication of the association of rs7219669 with the T-peak to T-end interval

The strongest associations of rs7219669 at chr17q24 and rs17749681 at chr16p13 with the TPE interval in the Health 2000 Study were subsequently analyzed in the FHS population. The clinical characteristics of the FHS population are also shown in Table 1. Of the 3 745 individuals from FHS eligible for the study after exclusion, 46 % ($n=1\,725$) were men. The mean age was 40.1 ± 8.9 years and the mean TPE interval was 95.6 ± 12.4 ms. The association of rs7219669 (MAF 0.45 in FHS) minor allele with TPE-interval shortening was replicated in the FHS study sample (-1.5 ms, $P=1.3\times 10^{-4}$), while the association of rs17749681 (MAF 0.42 in FHS) with TPE-interval prolongation did not replicate (-0.3 ms, $P=0.23$). The meta-analysis combining the data from the Health 2000 and the Framingham Heart Study for rs7219669 yielded an overall effect estimate of -1.7 ms ($P=5.7\times 10^{-14}$).

The variant rs7219669 is located ~350 kb downstream of the *KCNJ2* gene that encodes a cardiac inwardly-rectifying potassium channel Kir2.1 and underlies the long QT syndrome subtype 7²⁰ and the short QT syndrome subtype 3.²¹ Other genes in the region are unknown to be involved in cardiac electrophysiology.

DISCUSSION

This is the first reported genetic association study of the T-peak to T-end interval using a genome-wide approach. We report a novel association of the minor allele of a common variant rs7219669 on chr17q24 with TPE-interval shortening in two independent study populations. The common variant rs7219669 maps downstream of the inwardly rectifying cardiac potassium channel, which defects are established causes of congenital long- and short-QT syndromes.

A few gene variants, initially associated with QT interval, have been reported to affect TPE interval in the general population.^{7, 8} We have shown in a study population consisting of 5 890 participants from the Health 2000 Study that the minor allele of *KCNH2* K897T polymorphism is associated with a 1.2-ms shortening of the TPE interval and an intronic variant rs3807375 of the *KCNH2* gene with a 0.8-ms prolongation of the TPE interval.⁷ Similarly, the minor alleles of several *NOS1AP* gene variants (rs2880058, rs4657139, rs10918594, rs10494366) were associated with a 0.5-ms to 0.8-ms shortening of the TPE interval.⁷ A Japanese group has also reported an association of the minor allele of *KCNQ1* G643S variant with TPE-interval prolongation independently of significant QT interval prolongation.⁸ In the present GWA study, we were not able to detect significant association signals for these gene variants most likely due to the limited sample size. The ancestry difference between the Japanese and the current sample could also be a potential source of nonreplication.

There is a growing need for understanding modifiers of ventricular repolarization and arrhythmia susceptibility. Previously, several genetic association studies have reported common genetic variants that affect QT interval in the general population.²²⁻²⁵ A few gene variants affecting QT interval have also directly been associated with sudden cardiac death in patients with cardiovascular disease²⁶ and in general population.^{27, 28} These variants are located in or near *CASQ2*²⁶, *GPD1L*²⁶, *NOS1AP*^{26, 28}, *KCNQ1*²⁷ and *SCN5A*²⁷ genes that have a well-established role in cardiac electrophysiology. In addition, Pfeufer et al reported

a common variant rs17779747 near *KCNJ2* gene to be associated with QT-interval shortening.²³ Since this variant is not correlated with the rs7219669 of the current study ($r^2=0.162$), it is likely that these variants near *KCNJ2* gene represent independent effectors of cardiac repolarization. In the absence of additional supportive data, the association of the rs7219669 with *KCNJ2* gene remains speculative. However, the rs7219669 might influence regulatory elements such as transcription factor binding sites, DNA methylation or histone binding sites and thus affect *KCNJ2* gene expression.

Dispersion of repolarization is associated with reentrant ventricular arrhythmias in experimental studies.^{29, 30} In agreement with these studies, reports on patients with hypertension,¹ inherited arrhythmia disorders,⁴ cardiomyopathies³ and patients with myocardial infarction² have shown that prolongation of the TPE interval may increase arrhythmia susceptibility in clinical settings. Recently, prolongation of the TPE interval was independently associated with sudden cardiac death in a community study, and showed particular utility when the QTc interval was normal or not measureable due to a prolonged QRS complex.⁵ Since TPE interval is a heritable trait,⁶ genetic factors affecting TPE interval could ultimately mark individuals at higher risk for ventricular arrhythmias and sudden cardiac death in the general population.

STUDY STRENGTHS AND LIMITATIONS

The present study was carried out in two large independent population-based studies showing consistent results. However, the sample size is limited and larger study populations, possibly from different ethnic backgrounds, could reveal other TPE interval associated gene variants. The study focused solely on the electrocardiographic TPE interval that was measured by different methods in the two study samples, demonstrating that genetic association results are robust to these differences. The study did not include data on clinical outcomes, and therefore the clinical significance of the association of rs7219669 with TPE-interval shortening remains unclear.

CONCLUSION

We conclude that the minor allele of common variant rs7219669 is associated with TPE-interval shortening in two independent study populations and thus is a candidate to modulate arrhythmia susceptibility at the population level.

Acknowledgments

Johannes Kettunen is acknowledged for quality control of the genotype data and Ida Surakka for performing the imputations. Niina Eklund is acknowledged for producing the graphics.

SOURCES OF FINANCIAL SUPPORT: K.P., L.O., and M.V. were financially supported by the Finnish Foundation for Cardiovascular Research and K.P. also by the Orion-Farmos Research Foundation. M.P. was supported by the Finnish Academy SALVE program "Pubgensense" 129322 and the Finnish Foundation for Cardiovascular Research. V.S. was supported by the Academy of Finland (grants #129494 and #139635). K.K. was supported by grants from the Sigrid Juselius Foundation and Finnish Foundation for Cardiovascular Research. The Framingham Heart Study work was supported by the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine (Contract No. N01-HC-25195), its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278), and the Doris Duke Charitable Foundation (C.N.-C.) and Burroughs Wellcome Fund (C.N.-C.), based on analyses by Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project.

LIST OF ABBREVIATIONS

ECG electrocardiogram

GWA	genome-wide association
MAF	minor allele frequency
SNP	single nucleotide polymorphism
TPE	T-peak to T-end interval

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Figure 1. Manhattan plot of the Health 2000 Study showing genome-wide association results with the T-peak to T-end interval. * refers to the significant peak of rs7219669 on chr17q24.

Table 1

The clinical characteristics of the two study populations

	Health 2000 Study	Framingham Heart Study
n	1 870	3 745
Men, n (%)	902 (48 %)	1 725 (46 %)
Age, years	50.4 ± 10.9	40.1 ± 8.9
QT interval, ms	388.9 ± 29.7	415.4 ± 29.9
QTc interval (Bazett), ms	395.3 ± 22.4	419.8 ± 22.9
TPE interval, ms	73.6 ± 8.4	95.6 ± 12.4
Cornell voltage-duration product, mm·ms	1730.2 ± 554.1	1260.8 ± 436.4

Data are presented as mean ± SD for continuous variables and as numbers (percentages) for categorical variables. TPE refers to T-peak to T-end interval

Table 2

Single-nucleotide polymorphisms showing suggestive genome-wide association with the T-peak to T-end interval in the Health 2000 Study

SNP	Chr	Coded allele	Minor allele frequency	Beta	P
rs17749681	16p13	C	0.38	1.45	2.1×10^{-7}
rs7219669	17q24	T	0.38	-1.79	1.1×10^{-10}