A common variant near the *KCNJ2* gene is associated with T-peak to T-end interval

Annukka Marjamaa, MD, PhD,* Lasse Oikarinen, MD, PhD,† Kimmo Porthan, MD, PhD,† Samuli Ripatti, PhD,‡ Gina Peloso, PhD,§†† Peter A. Noseworthy, MD,§ Matti Viitasalo, MD, PhD,† Markku S. Nieminen, MD, PhD,† Lauri Toivonen, MD, PhD,† Kimmo Kontula, MD, PhD,*¶ Leena Peltonen, MD, PhD,‡# Aki S. Havulinna, DSc(Tech),# Antti Jula, MD, PhD,# Christopher J. O'Donnell, MD, MPH,**†† Christopher Newton-Cheh, MD, MPH,§** Markus Perola, MD, PhD,‡‖‡‡ Veikko Salomaa, MD, PhD,#

*From the *Research Program in Molecular Medicine, University of Helsinki, Helsinki, Finland, †Division of Cardiology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland, ‡Institute for Molecular Medicine Finland, FIMM, University of Helsinki, Helsinki, Finland, §Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, ‖University of Tartu, Estonian Genome Center, Tartu, Estonia, ¶Department of Medicine, University of Helsinki, Helsinki, Finland, #National Institute for Health and Welfare, Helsinki, Finland, **Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, ††NHLBI's Framingham Heart Study, National Institutes of Health, Bethesda, Maryland, and ‡‡Public Health Genomics Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland.*

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

OBJECTIVE To identify common genetic variants that affect the duration of the TPE interval in the general population.

METHODS We performed a genome-wide association study on 1870 individuals of Finnish origin participating in the Health 2000 Study. The TPE interval was measured from T-peak to T-wave end in leads II, V_2, and V_5 on resting electrocardiograms, 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 3745 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 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 2 studies was −1.7 ms ($P = 5.7 \times 10^{-14}$). The common variant rs7219669 maps downstream of the *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 Electrocardiogram; Repolarization; T wave; Gene; Polymorphism

ABBREVIATIONS **ECG** = electrocardiogram; **FHS** = Framingham Heart Study; **MAF** = minor allele frequency; **SNP** = single nucleotide polymorphism; **TPE** = T-peak to T-end

(Heart Rhythm 2012;9:1099–1103)

Leena Peltonen is deceased. Dr Porthan, Dr Oikarinen, and Dr Viitasalo were financially supported by the Finnish Foundation for Cardiovascular Research. Dr Porthan was also supported by the Orion-Farmos Research Foundation. Dr Perola was supported by the Finnish Academy SALVE program "Pubgensense" 129322 and the Finnish Foundation for Cardiovascular Research. Dr Salomaa was supported by the Academy of Finland (grant numbers 129494 and 139635). Dr Kontula 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 number N01-HC-25195), its contract with Affymetrix, Inc, for genotyping services (contract number N02-HL-6-4278), and the Doris Duke Charitable Foundation (to Dr Newton-Cheh) and Burroughs Wellcome Fund (to Dr Newton-Cheh), based on analyses by Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project.
Address for reprints and correspondence: Dr Annukka Marjamaa, MD, PhD, Research Program in Molecular Medicine, University of Helsinki,Biomedicum Helsinki, B327b, PO Box 700, 00029 Huch, Finland. E-mail address: Annukka.Marjamaa@helsinki.fi.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2012.02.019

Introduction

The interval from the peak of the T wave to the end of the T wave (T-peak to T-end [TPE] interval) on the electrocardiogram (ECG) is a measure of myocardial dispersion of repolarization. Increasing evidence suggests that the 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 the 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 by using a genome-wide association analysis and replication in independent study populations with well-characterized ECG phenotypes.

Methods

Study populations

The Health 2000 Study was a 2-stage stratified cluster sample of 8028 Finnish adults aged ≥30 years. The survey included comprehensive health interviews, physicians' clinical examinations, digital standard 12-lead ECG recordings from 6295 participants, and DNA samples from 6334 individuals.[9] The genome-wide analysis was carried out in a subset of 2212 original Health 2000 Study participants with metabolic syndrome or their matched controls. After quality-control procedures, 2138 genotyped individuals were available for the study. Subjects carrying Finnish long QT syndrome 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 QT-prolonging drugs (first category on drugs with the risk of *torsades de pointes*) (n = 129) were excluded.[7] The final study population consisted of 1870 individuals. The replication sample included 3745 participants from the third 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 Study and the FHS, standard 12-lead resting ECGs were recorded by using Marquette MAC 5000 ECG recorder (GE Marquette Medical Systems, Milwaukee, WI). In Health 2000 Study, as previously described,[7] TPE intervals were measured from digital ECGs by using a custom-made software and a previously validated algorithm.[12] The software measured QT and TPE intervals in each lead from a median QRS-T complex, which in each lead represents a digitally averaged complex from the full 10-second ECG recording. A single observer (K.P.) reviewed the measurements in a blinded fashion. In the FHS, 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 by using digital calipers on scanned ECGs. TPE-interval measurements were available in leads II, V_2, and V_5 in both study populations. The mean of the TPE interval in these leads was used in the analyses, which may optimize the precision of the measure. TPE intervals were corrected neither for heart rate nor for QT interval.[13]

Genome-wide analysis

Samples from the Health 2000 Study cohort were genotyped by using the Illumina Infinium HD Human 610-Quad BeadChip (Illumina, Inc, San Diego, CA). Probe signals were clustered into genotype groups by using the Illuminus algorithm9, and subsequent quality criteria for single nucleotide polymorphism (SNP) inclusion were as follows: a call rate of ≥95%, minor allele frequency (MAF) of ≥2%, and a HWE P value of $\geq 1 \times 10^{-4}$. 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 of >95%. After these quality-control procedures, 550,284 SNPs and 2138 genotyped individuals were available for the study. We imputed SNP genotype data by 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

By using linear regression analysis, we adjusted the mean TPE interval calculated from leads II, V_2, and V_5 for age, sex, and Cornell voltage-duration product (mm · ms, male: [RaVL + SV3] × QRS; female: [RaVL + SV3 + 8] × QRS), all of which were statistically significant covariates ($P < .05$). Cornell voltage-duration product is a measure of left ventricular

Table 1 The clinical characteristics of the 2 study populations

	Health 2000 Study	Framingham Heart Study
n	1870	3745
Sex: Man	902 (48)	1725 (46)
Age (y)	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 = T-peak to T-end; QTc = corrected QT.