RELATIONSHIP OF COMMON CANDIDATE GENE VARIANTS TO ELECTROCARDIOGRAPHIC T-WAVE PEAK TO T-WAVE END INTERVAL AND T-WAVE MORPHOLOGY PARAMETERS

Kimmo Porthan, MD[a], **Annukka Marjamaa, MD PhD**[b], **Matti Viitasalo, MD PhD**[a], **Heikki Väänänen, Lic Sc (Tech)**[c], **Antti Jula, MD PhD**[d], **Lauri Toivonen, MD PhD FHRS**[a], **Markku S Nieminen, MD PhD**[a], **Christopher Newton-Cheh, MD MPH**[g,h], **Veikko Salomaa, MD PhD**[e], **Kimmo Kontula, MD PhD**[f], and **Lasse Oikarinen, MD PhD**[a]

[a]Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland [b]Research Program in Molecular Medicine, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland [c]Department of Biomedical Engineering and Computational Science, Helsinki University of Technology, Espoo, Finland [d]National Institute for Health and Welfare, Turku, Finland [e]National Institute for Health and Welfare, Helsinki, Finland [f]Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland [g]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA [h]Cardiovascular Research Center & Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA

Abstract

BACKGROUND—Single-nucleotide polymorphisms (SNPs) in genes encoding cardiac ion channels and nitric oxide synthase 1 adaptor protein (NOS1AP) are associated with electrocardiographic (ECG) QT-interval duration, but the association of these SNPs with new prognostically important ECG measures of ventricular repolarization has been unknown.

OBJECTIVE—Our aim was to examine the relationship of SNPs to ECG T-wave peak to T-wave end (TPE) interval and T-wave morphology parameters.

METHODS—We studied 5,890 adults attending the Health 2000 Study, a Finnish epidemiological survey. TPE interval and four T-wave morphology parameters were measured from digital 12-lead ECGs and related to those seven SNPs showing a phenotypic effect on QT-interval duration in the Health 2000 Study population.

RESULTS—In multivariable analyses, the *KCNH2* K897T minor allele was associated with a 1.2 ms TPE-interval shortening (*P*=.00005) and the *KCNH2* intronic rs3807375 minor allele was associated with a 0.8 ms TPE-interval prolongation (*P*=.001), whereas the *KCNE1* D85N variant had no TPE-interval effect (*P*=.20). *NOS1AP* minor alleles (rs2880058, rs4657139, rs10918594,

rs10494366) were associated with shorter TPE interval (effects from 0.5 to 0.8 ms, *P* from .032 to .002), which resulted from their stronger effects on QT_{peak} than QT_{end} interval. None of the SNPs showed a consistent association with T-wave morphology parameters.

CONCLUSIONS—*KCNH2* K897T and rs3807375 as well as the four studied *NOS1AP* variants have modest effects on ECG TPE interval but are not related to T-wave morphology measures. The previously observed prognostic value of T-wave morphology parameters is unlikely to be based on these SNPs.

Keywords

electrocardiography; epidemiology; genetics; genetic polymorphism; ion channels; nitric oxide synthase; repolarization; T wave

Introduction

In monogenic repolarization-based arrhythmia disorders, such as long QT syndrome (LQTS), mutations in myocardial ion channel genes generate the arrhythmogenic substrate.[1] Common ion channel gene variants, such as single-nucleotide polymorphisms (SNPs), are associated with modest alterations in electrocardiographic (ECG) QT-interval duration, and may further modify repolarization-related arrhythmia vulnerability.[1-6] Additionally, genetic variation in nitric oxide synthase 1 adaptor protein gene (*NOS1AP*) is associated with QT interval[6,7] and, more importantly, has been associated with increased risk for clinical symptoms and more severe disease in a LQTS type 1 founder population[8] as well as with increased risk for sudden cardiac death in a sample from the general population.[9] The risk for sudden cardiac death was, however, independent of QT-interval duration in multivariable analyses,[9] raising the possibility that other ECG repolarization measures than QT interval might better reveal the increased risk.

The T wave is generated by myocardial voltage gradients during the repolarization phase of cardiomyocyte action potentials.[10,11] QT interval is a measure of repolarization duration, but may not reveal other changes during the repolarization process. T-wave peak to T-wave end (TPE) interval measures terminal repolarization, and has experimentally been linked to arrhythmogenic repolarization dispersion in the myocardium.[10,12,13] In addition, several new ECG repolarization measures characterizing T-wave morphology have been introduced.[14,15] In fact, in the general population T-wave morphology parameters seem to be more useful than other ECG repolarization measures in mortality risk assessment.[16] In the present study we examined the association of several SNPs with ECG TPE interval and T-wave morphology parameters to characterize more comprehensively the effects of the defined SNPs on ventricular repolarization in the large population-based Health 2000 Study.

Method

Study population

The study population was derived from an epidemiological survey, the Health 2000 Study, conducted in Finland in 2000–2001. The study population, drawn from the Finnish Population Information System, was a two-stage stratified cluster sample of 8,028 Finnish adults aged ≥30 years. The Health 2000 Study included a home interview, a comprehensive health examination with questionnaires, measurements (e.g. height, weight, blood pressure, ECG), and a physician's clinical examination. Definitions of hypertension, coronary heart disease, myocardial infarction, and diabetes in the current study have been published elsewhere.[16] Heart failure classification in the survey was based on hospital diagnoses, health interview, physician's clinical examination, and medication use for heart failure. Probable and certain

diagnoses of heart failure were included in the current study. The Health 2000 Study protocol is available online,[17] and was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital Region. All participants gave their signed informed consent.

Deoxyribonucleic acid samples were collected from 6,334 Health 2000 Study subjects, and ECGs were available from 6,292 subjects. From the present study, we excluded subjects carrying one of four Finnish LQTS founder mutations (n=27), ECGs with Minnesota coding showing Wolff-Parkinson-White syndrome (n=1), paced rhythm (n=4), atrial fibrillation (n=93), atrial flutter (n=1), complete left bundle branch block (n=56), complete right bundle branch block (n=61), or low-quality ECG (n=8). We also excluded subjects who used medication with possible effect on QT-interval duration (n=151). These were the drugs listed in the first category ("Drugs with Risk of Torsades de Pointes") on the website www.qtdrugs.org (accessed November 2007) and digoxin, which shortens QT interval. The present study thus included 5,890 individuals.

Electrocardiographic measurements

A digital standard 12-lead ECG was recorded with a Marquette MAC 5000 electrocardiograph (GE Marquette Medical Systems, Milwaukee, Wisconsin, USA). All leads were simultaneous recordings, and a median QRS-T complex was used for analyses.[18] We used QT Guard software (GE Marquette Medical Systems) to measure heart rate and principal component analysis (PCA) ratio, and custom-made software for all other measurements. The reproducibility of our repolarization measurements was good and has been previously published.[18] Left ventricular hypertrophy was considered to be present if Sokolow-Lyon voltage >3.5 mV or Cornell voltage-duration product >244 mV×ms, or both criteria were observed.

TPE intervals—We performed TPE-interval measurements based on a previously described and validated algorithm.[19,20] The software calculated TPE interval from T-wave peak to T-wave end in each lead. A single observer (K.P.) reviewed measurements on-screen in a blinded fashion. Leads with low signal-to-noise ratio or flat T waves were excluded from TPE-interval analyses, and the mean number of TPE-interval measurements per ECG was 10.3±1.7. We used the maximum TPE interval from precordial leads for analyses. TPE intervals were not corrected for heart rate.[21] SNP effects on QT_{peak} and QT_{end} intervals were analyzed from the lead with the maximum precordial TPE interval. QT intervals were heart rate-adjusted with the nomogram method as previously described.[16]

T-wave morphology parameters—The automatic calculation of T-wave morphology parameters has been published in detail previously.[16] In brief, the PCA ratio was calculated as the ratio of the second to first eigenvalues of the spatial T-wave vector with an increase in PCA ratio indicating more complex T-wave morphology.[14] After singular value decomposition of eight independent ECG leads (I, II, V_1-V_6), T-wave morphology dispersion (TMD) measures the average angle between T-wave reconstruction vector pairs, with higher values indicating increasing differences in T-wave morphology among the leads.[16] Total cosine R-to-T (TCRT) measures the deviation between potential directions during depolarization and repolarization phases, with lower values indicating increasing angle between R- and T-wave vectors.[16] The vector magnitude of the fourth to eighth eigenvalues gives the absolute T-wave residuum (TWR). Higher TWR values indicate increasing non-dipolar ECG signal content and are expected to represent higher degree of ventricular repolarization heterogeneity,[15] whereas PCA ratio, TCRT, and TMD reflect changes in dipolar ECG signal content. In the present study, T-wave morphology parameters showed nonsignificant or only very weak correlations to heart rate (absolute *r* values from 0.005 to 0.08).

Genetic analyses

We have recently published the relationship between several LQTS gene and *NOS1AP* SNPs to QT_{end} interval.[6] In the present study, we included *KCNH2* rs1805123 (K897T) and rs3807375, *KCNE1* rs1805128 (D85N), and four *NOS1AP* SNPs (rs2880058, rs4657139, rs10918594, rs10494366), based on their shortening or prolonging effects on QT_{end} interval in the Health 2000 Study population.[6] For rs1805123, genotyping was performed using a TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, California, USA) and for all other SNPs using Sequenom MALDI-TOF mass spectrometry (MassArray Compact Analyzer, Sequenom Inc, San Diego, California, USA).

Statistics

Analyses were performed with SPSS software 15.0 (SPSS Inc., Chicago, Illinois, USA). The prevalence estimates of genotypes were derived from the weighted study population as described previously.[17] We analyzed the association between ECG repolarization parameters and clinical variables including: gender, age, current smoking status, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, hypertension, coronary heart disease, previous myocardial infarction, heart failure, diabetes mellitus, ECG left ventricular hypertrophy status, and Cornell voltage-duration product (as a continuous variable). Of these clinical variables, gender, age, systolic blood pressure, coronary heart disease, previous myocardial infarction, and Cornell voltage-duration product were selected as covariates for regression analyses ($P<.001$ for the association with repolarization parameters for most of the variables). Using a stepwise linear regression model, each repolarization parameter was adjusted for the clinical covariates. The output residuals were saved and used as the dependent variable in further linear regression analyses with the genotypes as the independent variable. In additive genetic models, we transformed each genotype to a continuous variable that corresponded to the number of minor alleles (0, 1, 2). In genotypic genetic models, two degrees of freedom test was used, and the heterozygote and minor homozygote genotypes were converted to two dichotomous variables and the major homozygote genotype was the reference. The results are shown for additive genetic models. Appropriateness of the additive model was confirmed by evaluating the genotype-specific means for residuals of repolarization parameters. Non-normal variable distributions of PCA ratio, TMD, TCRT, and TWR were normalized in regression analyses. The PCA ratio, TMD, and TWR were normalized with natural-logarithmic transformation. The TCRT was normalized with the Blom method[22] because its distribution was not normalized with the logarithmic transformation. All SNPs were tested for Hardy-Weinberg equilibrium with the Chisquare test. For all tests, two-tailed $P<.05$ was considered significant.

Results

Genotyping call rates ranged from 97.6% to 99.9% and all SNPs were in Hardy-Weinberg equilibrium ($P>.01$). Table 1 shows the clinical characteristics and mean values of ECG repolarization measures in the study population.

Relationship of SNPs to TPE interval

Table 2 shows TPE intervals by genotype in the study population and SNP effects on TPE interval from multivariable regression analyses. A 1.2 ms TPE-interval shortening was observed per *KCNH2* K897T minor allele and a 0.8 ms prolongation per *KCNH2* rs3807375 minor allele. *KCNE1* D85N did not have an effect on TPE interval. For the four *NOS1AP* SNPs with strong linkage disequilibrium (r^2 between 0.77 and 0.97), minor alleles were associated with TPE-interval shortening, with the effect varying from 0.5 to 0.8 ms. The results were unchanged when TPE interval was measured from a single lead (V_3) (data not shown). The results were also tested with the genotypic genetic models, and this did not change the results.

Analyses after excluding a total of 1,355 subjects with coronary heart disease, previous myocardial infarction, heart failure, or ECG left ventricular hypertrophy did not alter the results (data not shown).

SNP effects on QT_{peak} and QT_{end} intervals were analyzed for the SNPs that were significantly associated with TPE interval. Figure 1 shows that both *KCNH2* K897T and *NOS1AP* rs10918594 were associated with prolongation of QT_{end} interval. For *NOS1AP*, however, the association with QT_{peak} interval was stronger than with QT_{end} interval, resulting in the shortening of TPE interval. The results remained the same when QT intervals were analyzed from a single lead (V_3) and from the lead with the maximum precordial QT_{end} interval (data not shown).

Relationship of SNPs to T-wave morphology parameters

We studied the relationship of SNPs to T-wave morphology parameters (PCA ratio, TMD, TCRT, TWR). The multivariable regression analyses showed that *KCNH2* K897T minor allele was associated with a 0.03 unit decrease in normalized TWR (P=.04), *NOS1AP* rs4657139 minor allele was associated with a 0.04 unit decrease in normalized TCRT (P=.04), and that *NOS1AP* rs10494366 minor allele was associated with a 0.04 unit decrease in normalized TCRT (P=.03). For all other SNPs, the results were nonsignificant (both allelic and genotypic genetic models tested, data not shown). When the three SNPs with significant results were tested with genotypic models, only the relationship between *KCNH2* K897T and TWR was statistically significant (P=.04). Analyses after excluding study subjects with coronary heart disease, previous myocardial infarction, heart failure, or ECG left ventricular hypertrophy showed that *KCNH2* K897T minor allele was associated with a 0.04 unit decrease in normalized TMD (P=.02) and normalized TWR (P=.02). These associations remained significant also in genotypic models, but for all other SNPs, the results were nonsignificant (data not shown).

Discussion

Main findings

Our results show that *KCNH2* K897T minor allele C is associated with shorter ECG TPE interval and *KCNH2* intronic rs3807375 minor allele A is associated with longer ECG TPE interval. These are consistent with their associations with shorter and longer QT_{end} intervals, respectively, as previously shown.[6] *NOS1AP* minor alleles are associated with shorter TPE interval. This is opposite in direction to the effects of the same alleles on the duration of QT_{end} interval and seems to be resulted from their stronger effect on QT_{peak} than QT_{end} interval. None of the SNPs showed a consistent association with T-wave morphology parameters.

ECG TPE interval and T-wave morphology measures

Dispersion of ventricular repolarization predisposes to repolarization-related arrhythmogenesis.[10] In experimental studies using myocardial wedge preparations, TPE interval has been show to correlate with transmural dispersion of repolarization.[10,11,23] In other studies, TPE interval has been shown to be a measure of global dispersion of repolarization. [12,13] In an ambulatory ECG study of LQTS type 1 and 2 patients, TPE interval behaviour paralleled experimental and computer-simulated findings in transmural dispersion of repolarization in loss-of-function of the slow (I_{Ks}) and rapid (I_{Kr}) components of the delayed rectifier current, which cause LQTS type 1 and 2, respectively.[24]

T-wave morphology parameters, characterizing the three-dimensional morphology of the T wave, have been shown to provide prognostic information on survival in the general population. [14-16] Of note, in the Health 2000 Study population T-wave morphology parameters, but not

heart-rate corrected QT_{end} interval, contained independent prognostic information on mortality, and the prognostic value was specifically related to cardiovascular mortality.[16]

Several SNPs of *KCNE1, KCNH2*, and *NOS1AP* have been shown to be associated with longer QT_{end} interval.[1] The recently observed increased risk of sudden death with *NOS1AP* variants in a general population sample was independent of the duration of QT_{end} interval, however.[9] Thus, we explored the effects of these variants on TPE interval and T-wave morphology parameters.

KCNH2 K897T and rs3807375, and repolarization measures

Experimental studies have shown that the *KCNH2* K897T substitution has multiple effects on cellular electrophysiology,[2,25-27] suggesting that the net effect of these changes on ECG ventricular repolarisation is difficult to predict. Our present study shows that K897T variant shortens ECG TPE interval but does not consistently alter T-wave morphology parameters. In the Health 2000 Study population analyzing the age-, gender- and heart rate-adjusted QT interval, we have shown this polymorphism to shorten QT_{end} interval by 2.6 ms per minor allele.[6] Also in several other studies, this polymorphism has been shown to slightly shorten QT_{end} interval,[2-5] but conflicting results do exist.[28] In previous reports, the impact of the minor K897T allele has been suggested to be both protective and harmful, but sample sizes in these reports have been small.[29,30]

There are no experimental studies characterizing the functional properties of *KCNH2* intronic SNP rs3807375 on myocardial repolarization. We observed that the minor allele of this variant prolongs TPE interval, but it has no effects on T-wave morphology parameters. Previously this variant has been reported to prolong QT_{end} interval,[5] a finding also observed in the Health 2000 Study population showing a 1.6 ms prolonging effect per minor allele.[6] Since the prolongation of QT_{end} and TPE interval on the resting ECG is a typical feature in LQTS type 2 caused by reduced I_{Kr} current,[23,24,31] our ECG findings suggest that rs3807375 might reduce the repolarization reserve.

KCNE1 D85N and repolarization measures

KCNE1 D85N polymorphism causes variation in minK, which is the regulatory subunit of the I_{Ks} channel.[32] Experimental studies have suggested that the minor D85N allele reduces I_{Ks} current.[33] The 85N allele may thus predispose to acquired LQTS and modify the clinical expression of congenital LQTS.[34] In experimental LQTS type 1 models, I_{Ks} block prolongs action potential duration homogeneously, and therefore does not increase transmural dispersion at rest, but does so in conjunction with β-adrenergic stimulation.[31]

In a previous analysis from the Health 2000 Study population, we observed a substantial 10.5 ms prolongation in QT_{end} interval per each *KCNE1* D85N minor allele.[6] The present results show that, despite the marked prolongation of QT_{end} interval observed in our prior study,[6] this variant has no effect on ECG TPE interval or T-wave morphology measures. In ambulatory ECG recordings among LQTS type 1 patients, TPE interval increased significantly only at high heart rates.[24] Thus, our findings in resting ECGs showing D85N variant to prolong QT_{end} but not TPE interval are consistent with reduced I_{Ks} current. It remains to be studied, whether the D85N polymorphism is associated with a prolongation of TPE interval during physical exercise.

NOS1AP variants and repolarization measures

In experimental studies, overexpression of CAPON, the product of *NOS1AP* gene, results in up-regulation of NOS1-NO signalling pathways, leading to reduced $I_{Ca,L}$ and enhanced I_{Kr} currents, and to shortened action potential.[35] Postulating that genetic variants in *NOS1AP* lead

to lower CAPON levels, increased $I_{Ca,L}$ and decreased I_{Kr} currents with prolonged action potential are expected.[8] In previous population studies, including our recent study in the Health 2000 Study population, the minor alleles of several *NOS1AP* variants have been shown to be associated with longer QT_{end} interval.[6,7]

Recently, Crotti et al. reported that *NOS1AP* variants rs4657139 (one of the SNPs included in the present study) and rs16847548 were associated with a greater prolongation QT_{end} interval, increased risk for symptoms, and greater probability for cardiac arrest and sudden death in a South African LQTS type 1 founder population.[8] They suggested that increased $I_{Ca,L}$ current might be associated with arrhythmogenic consequences in LQTS type 1 patients.[8] On the other hand, Kao et al. reported that *NOS1AP* variants rs16847548 and rs12567209 were associated with sudden cardiac death in a large cohort of United States white adults, but the effect was independent of the duration of QT_{end} interval in multivariable analyses, however.[9] These authors suggested that either QT_{end} interval might not be a sufficient measure of ventricular repolarization or the prognostic value of *NOS1AP* variants might be mediated by other mechanisms than repolarization.[9]

In the present study, the examined minor alleles of the *NOS1AP* variants were associated with shorter TPE interval but had no effects on T-wave morphology parameters. With a supposed decreased I_{Kr} current, TPE-interval shortening was an unexpected finding. Interestingly, our results suggest a stronger prolonging effect of *NOS1AP* SNPs on QT_{peak} than QT_{end} interval. Whether the shortening of TPE interval is mediated by increased $I_{Ca,L}$ or by some other mechanism remains to be studied.

Limitations

Our results may not be applicable to populations from different genetic backgrounds or to other races, and replication of the observed associations in another, independent cohort is warranted. The association between the SNPs and TPE interval appears weak and thus its clinical significance remains to be studied. Our analyses included four strongly correlating *NOS1AP* SNPs, and some other SNPs not examined in the present study may have different repolarization effects and prognostic value.[9] The exact electrophysiological basis of T-wave morphology parameters is currently unknown.

Conclusion

Our results show that *KCNH2* K897T minor allele is associated with shortening, and *KCNH2* rs3807375 minor allele is associated with prolongation of ECG TPE interval. *KCNE1* D85N has no effect on TPE interval. The studied *NOS1AP* minor alleles prolong more QT_{peak} than QT_{end} interval, with the net effect being shorter TPE interval. None of the studied SNPs showed consistent association with ECG T-wave morphology parameters, suggesting that these polymorphisms do not mediate the observed prognostic value of T-wave morphology parameters in the Health 2000 Study. The studied repolarization parameters seem not to clarify the association between *NOS1AP* variants and sudden cardiac death.

Acknowledgments

None.

List of manuscript abbreviations

ECG	electrocardiographic
LQTS	long QT syndrome
NOS1AP	nitric oxide synthase 1 adaptor protein gene
PCA	principal component analysis
SNP	single-nucleotide polymorphism
TCRT	total cosine R-to-T
TMD	T-wave morphology dispersion
TPE	T-wave peak to T-wave end
TWR	T-wave residuum

References

1. Noseworthy PA, Newton-Cheh C. Genetic determinants of sudden cardiac death. Circulation 2008;118:1854–1863. [PubMed: 18955676]

2. Bezzina CR, Verkerk AO, Busjahn A, et al. A common polymorphism in KCNH2 (HERG) hastens cardiac repolarization. Cardiovasc Res 2003;59:27–36. [PubMed: 12829173]

3. Gouas L, Nicaud V, Berthet M, et al. Association of KCNQ1, KCNE1, KCNH2 and SCN5A polymorphisms with QTc interval length in a healthy population. Eur J Hum Genet 2005;13:1213–1222. [PubMed: 16132053]

4. Pfeufer A, Jalilzadeh S, Perz S, et al. Common variants in myocardial ion channel genes modify the QT interval in the general population: results from the KORA study. Circ Res 2005;96:693–701. [PubMed: 15746444]

5. Newton-Cheh C, Guo CY, Larson MG, et al. Common genetic variation in KCNH2 is associated with QT interval duration: the Framingham Heart Study. Circulation 2007;116:1128–1136. [PubMed: 17709632]

6. Marjamaa A, Newton-Cheh C, Porthan K, et al. Common candidate gene variants are associated with QT interval duration in the general population. J Int Med 2009;265:448–458.

7. Arking DE, Pfeufer A, Post W, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nat Genet 2006;38:644–651. [PubMed: 16648850]

8. Crotti L, Monti MC, Insolia R, et al. NOS1AP Is a Genetic Modifier of the Long-QT Syndrome. Circulation 2009;120:1657–1663. [PubMed: 19822806]

9. Kao WH, Arking DE, Post W, et al. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. Circulation 2009;119:940–951. [PubMed: 19204306]

10. Yan G-X, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928–1936. [PubMed: 9799215]

11. Antzelevitch C. Cellular basis for the repolarization waves of the ECG. Ann N Y Acad Sci 2006;1080:268–281. [PubMed: 17132789]

12. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol 1995;25:746–752. [PubMed: 7860924]

13. Opthof T, Coronel R, Wilms-Schopman FJ, et al. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm 2007;4:341–348. [PubMed: 17341400]

14. Okin PM, Devereux RB, Fabsitz RR, Lee ET, Galloway JM, Howard BV. Principal component analysis of the T wave and prediction of cardiovascular mortality in American Indians: the Strong Heart Study. Circulation 2002;105:714–719. [PubMed: 11839627]

15. Zabel M, Malik M, Hnatkova K, et al. Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. Circulation 2002;105:1066–1070. [PubMed: 11877356]

16. Porthan K, Viitasalo M, Jula A, et al. Predictive value of electrocardiographic QT interval and T-wave morphology parameters for all-cause and cardiovascular mortality in a general population sample. Heart Rhythm 2009;6:1202–1208. [PubMed: 19632634]

17. Aromaa, A.; Koskinen, S., editors. Health and functional capacity in Finland. Baseline results of the Health 2000 Health Examination Survey. Publications of the National Public Health Institute; Helsinki: [Accessed September 18, 2008]. Publication Number B12/2004Available at http://www.terveys2000.fi/julkaisut/baseline.pdf

18. Porthan K, Virolainen J, Hiltunen TP, et al. Relationship of electrocardiographic repolarization measures to echocardiographic left ventricular mass in men with hypertension. J Hypertens 2007;25:1951–1957. [PubMed: 17762661]

19. Oikarinen L, Paavola M, Montonen J, et al. Magnetocardiographic QT interval dispersion in postmyocardial infarction patients with sustained ventricular tachycardia: validation of automated QT measurements. Pacing Clin Electrophysiol 1998;21:1934–1942. [PubMed: 9793090]

20. Hekkala A-M, Väänänen H, Swan H, Oikarinen L, Viitasalo M, Toivonen L. Reproducibility of computerized measurements of QT interval from multiple leads at rest and during exercise. Ann Noninvasive Electrocardiol 2006;11:318–326. [PubMed: 17040280]

21. Andersen MP, Xue JQ, Graff C, Kanters JK, Toft E, Struijk JJ. New descriptors of T-wave morphology are independent of heart rate. J Electrocardiol 2008;41:557–561. [PubMed: 18804787]

22. Blom, G. Statistical estimates and transformed beta variables. John Wiley & Sons, Inc.; New York: 1958.

23. Gima K, Rudy Y. Ionic current basis of electrocardiographic waveforms: a model study. Circ Res 2002;90:889–896. [PubMed: 11988490]

24. Viitasalo M, Oikarinen L, Swan H, et al. Ambulatory electrocardiographic evidence of transmural dispersion of repolarization in patients with long-QT syndrome type 1 and 2. Circulation 2002;106:2473–2478. [PubMed: 12417545]

25. Anson BD, Ackerman MJ, Tester DJ, et al. Molecular and functional characterization of common polymorphism in HERG (KCNH2) potassium channels. Am J Physiol Heart Circ Physiol 2004;286:H2434–H2441. [PubMed: 14975928]

26. Paavonen KJ, Chapman H, Laitinen PJ, et al. Functional characterization of the common amino acid 897 polymorphism of the cardiac potassium channel KCNH2 (HERG). Cardiovasc Res 2003;59:603–611. [PubMed: 14499861]

27. Gentile S, Martin N, Scappini E, Williams J, Erxleben C, Armstron DL. The human ERG1 channel polymorphism, K897T, creates a phosphorylation site that inhibits channel activity. Proc Natl Acad Sci U S A 2008;105:14704–14708. [PubMed: 18791070]

28. Pietilä E, Fodstad H, Niskasaari E, et al. Association between HERG K897T polymorphism and QT interval in middle-aged Finnish women. J Am Coll Cardiol 2002;40:511–514. [PubMed: 12142119]

29. Crotti L, Lundquist AL, Insolia R, et al. KCNH2-K897T is a genetic modifier of latent congenital long-QT syndrome. Circulation 2005;112:1251–1258. [PubMed: 16116052]

30. Zhang X, Chen S, Zhang L, et al. Protective effect of KCNH2 single nucleotide polymorphism K897T in LQTS families and identification of novel KCNQ1 and KCNH2 mutations. BMC Med Genet 2008;9:87. [PubMed: 18808722]

31. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long QT-syndrome: effect of β-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsades de pointes. Circulation 1998;98:2314–2322. [PubMed: 9826320]

32. Lehmann-Horn F, Jurkat-Rott K. Voltage-Gated Ion Channels and Hereditary Disease. Physiol Rev 1999;79:1317–1372. [PubMed: 10508236]

33. Westenskow P, Splawski I, Timothy KW, Keating MT, Sanguinetti MC. Compound mutations: a common cause of severe long-QT syndrome. Circulation 2004;15:1834–1841. [PubMed: 15051636]

34. Nishio Y, Makiyama T, Itoh H, et al. D85N, a KCNE1 polymorphism, is a disease-causing gene variant in long QT syndrome. J Am Coll Cardiol 2009;54:812–819. [PubMed: 19695459]

35. Chang KC, Barth AS, Sasano T, et al. CAPON modulates cardiac repolarization via neuronal nitric oxide synthase signaling in the heart. Proc Natl Acad Sci U S A 2008;105:4477–4482. [PubMed: 18337493]
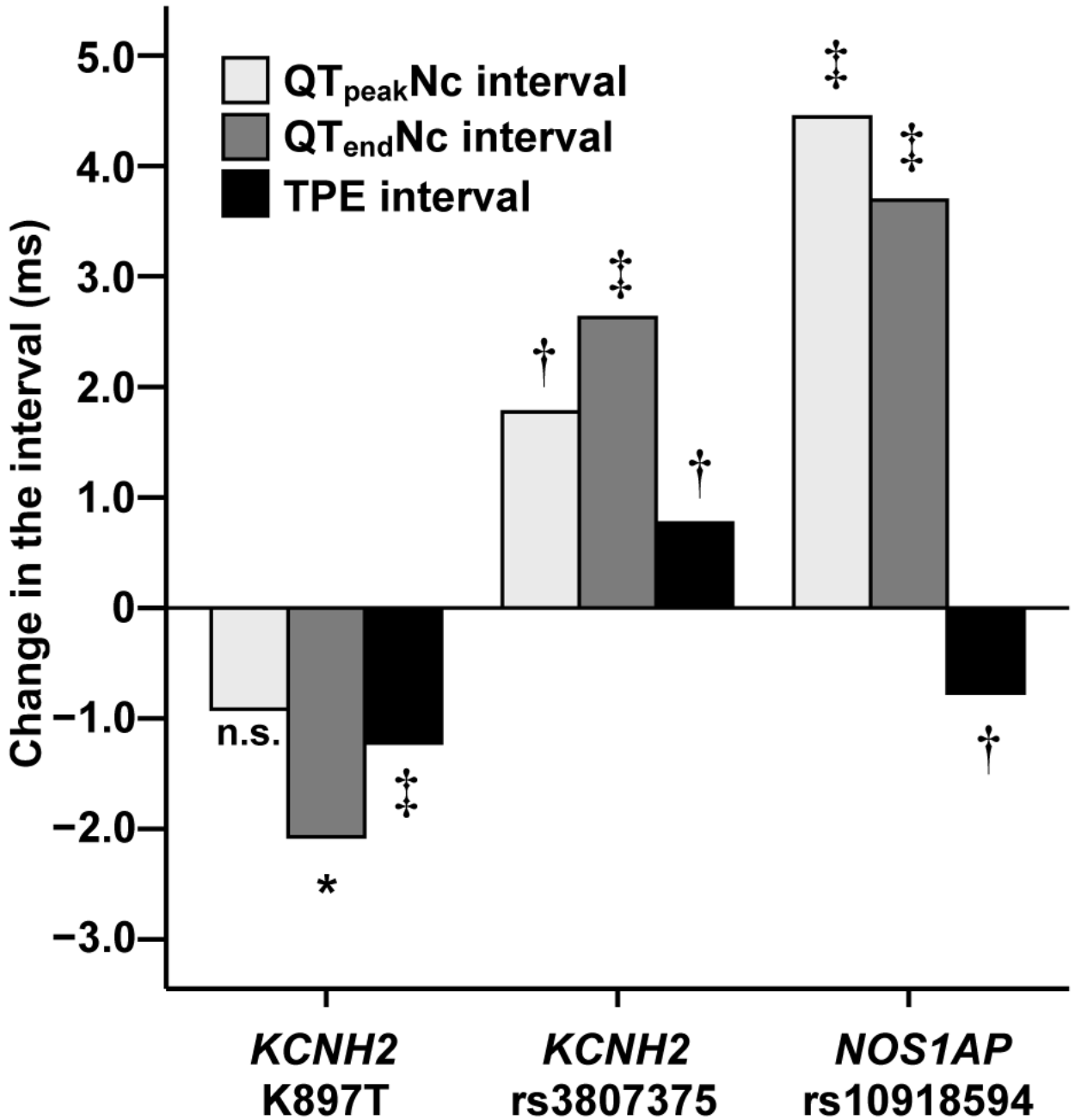
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Figure 1.
Effect of *KCNH2* K897T, *KCNH2* rs3807375, and *NOS1AP* 10918594 SNPs on electrocardiographic QT_{peak}, QT_{end}, and TPE interval. Values are differences from major homozygotes per one minor allele. Because of similarity of the results for all other *NOS1AP* SNPs, results are shown only for rs10918594. *P<.05, †P<.01, ‡P<.0001. Nc=nomogram-corrected for heart rate, n.s.=nonsignificant, SNP=single-nucleotide polymorphism, TPE=T-wave peak to T-wave end.

Table 1

Clinical characteristics and electrocardiographic repolarization measures (n=5,890)

Men (%)	45.2
Age (years)	52.1±14.3
Current smoking (%)	21.9
Body mass index (kg/m^2)	26.9±4.7
Heart rate (beats/minute)	63.3±10.7
Systolic blood pressure (mmHg)	134.2±21.0
Diastolic blood pressure (mmHg)	81.9±11.0
Hypertension (%)	46.8
Coronary heart disease (%)	6.6
Previous myocardial infarction (%)	2.3
Heart failure (%)	1.1
Diabetes mellitus (%)	5.6
ECG left ventricular hypertrophy (%)	17.8
TPE interval[*] (ms)	83.4±12.5
PCA ratio (%)	15.5±8.4
TMD (°)	14.6±13.4
TCRT (unitless)	0.36±0.52
TWR (technical units)	16,810±22,749

[*] Maximum precordial TPE interval. Values are mean±SD for continuous variables and percentages for categoric variables. PCA=principal component analysis, TCRT=total cosine R-to-T, TMD=T-wave morphology dispersion, TPE=T-wave peak to T-wave end interval, TWR=T-wave residuum.

Table 2

TPE intervals by genotype and effect of SNPs on electrocardiographic TPE interval

Gene	SNP	Allele* and amino acid changes	Major homozygotes		Heterozygotes		Minor homozygotes		Minor allele effect§	
			TPE† (ms)	%	TPE† (ms)	%	TPE† (ms)	%	ΔTPE† (ms)	P
KCNH2	rs1805123	A→C, K897T	83.8	67.9	82.5	28.8	81.6	3.3	−1.2	.00005
	rs3807375	G→A	82.7	32.4	83.7	49.4	84.1	18.2	+0.8	.001
KCNE1	rs1805128	G→A, D85N	83.4	97.3	81.7	2.6	83.9	0.1	−1.3	.20
NOS1AP	rs2880058	A→G	83.7	42.3	83.4	45.5	82.1	12.2	−0.6	.01
	rs4657139	T→A	83.6	41.3	83.5	46.1	82.1	12.6	−0.5	.03
	rs10918594	C→G	83.9	43.8	83.3	44.0	82.0	12.3	−0.8	.002
	rs10494366	T→G	83.7	41.6	83.4	45.7	82.3	12.7	−0.6	.02

Values are mean.

*
Major→minor allele.

†Maximum precordial TPE interval. Percentages refer to prevalence estimates.

§Additive genetic model with the values representing differences from major homozygotes per one minor allele (adjustment for gender, age, systolic blood pressure, coronary heart disease, previous myocardial infarction, Cornell voltage-duration product). SNP=single nucleotide polymorphism, TPE=T-wave peak to T-wave end interval.