American Heart Association®

Effect of Sex and Underlying Disease on the Genetic Association of QT Interval and Sudden Cardiac Death

Rebecca N. Mitchell, PhD; Foram N. Ashar, PhD; Marjo-Riitta Jarvelin, MD, PhD; Philippe Froguel, MD, PhD; Nona Sotoodehnia, MD, MPH; Jennifer A. Brody, BA; Sylvain Sebert, PhD; Heikki Huikuri, MD; John Rioux, PhD; Philippe Goyette, PhD; Charles E. Newcomb, BS; M. Juhani Junttila, MD; Dan E. Arking, PhD

Background—Sudden cardiac death (SCD) accounts for ≈300 000 deaths annually in the United States. Men have a higher risk of SCD and are more likely to have underlying coronary artery disease, while women are more likely to have arrhythmic events in the setting of inherited or acquired QT prolongation. Moreover, there is evidence of sex differences in the genetics of QT interval duration. Using sex- and coronary artery disease–stratified analyses, we assess differences in genetic association between longer QT interval and SCD risk.

Methods and Results—We examined 2282 SCD subjects and 3561 Finnish controls. The SCD subjects were stratified by underlying disease (ischemic versus nonischemic) and by sex. We used logistic regression to test for association between the top QT interval–associated single-nucleotide polymorphism, rs12143842 (in the *NOS1AP* locus), and SCD risk. We also performed Mendelian randomization to test for causal association of QT interval in the various subgroups. No statistically significant differences were observed between the sexes for associations with rs12143842, despite the odds ratio being higher in females across all subgroup analyses. Consistent with our hypothesis, female non-ischemics had the highest odds ratio point estimate for association between rs12143842 and SCD risk and male ischemics the lowest odds ratio point estimate (*P*=0.036 for difference). Similar trends were observed for the Mendelian randomization analysis.

Conclusions—While individual subgroup comparisons did not achieve traditional criteria for statistical significance, this study is consistent with the hypothesis that the causal association of longer QT interval on SCD risk is stronger in women and nonischemic individuals. (***J Am Heart Assoc***. 2019;8:e013751. DOI: 10.1161/JAHA.119.013751.)

Key Words: genetic association • Mendelian randomization • QT interval electrocardiography • sex-specific • sudden cardiac death

Sudden cardiac death (SCD) is among the leading causes of death in the United States, affecting ≈300 000 individuals annually.[1] SCD occurs as a result of multiple underlying disease pathologies, including heart diseases such as coronary artery disease and cardiomyopathies, as well as primary electrical defects.[2] Men have a higher risk of SCD than women,[3,4] and furthermore, the underlying cardiac pathology differs between the sexes. Coronary artery disease, the common underlying cause of SCD, is more common in men than in women. By contrast, nonischemic pathology, such as primary myocardial fibrosis, valvular heart disease, and arrhythmogenic right ventricular cardiomyopathy, occurs more commonly in women with SCD compared with men with SCD.[5–7] SCD is often the first manifestation of heart disease,

<div style="border:1px solid red">

Clinical Perspective

What Is New?

- Our study investigated the differences in genetic and causal associations between longer QT interval and SCD risk between SCD individuals with autopsy-confirmed ischemic and nonischemic underlying disease.
- We also investigated differences in genetic and causal associations between longer QT interval and SCD risk between men and women.

What Are the Clinical Implications?

- While not achieving traditional cutoffs for statistical significance, our results are consistent with the hypothesis that the causal association of longer QT interval on SCD risk is stronger in women and nonischemic individuals.

</div>

particularly for women; several studies have found that women are less likely than men to have a prior history of known cardiac disease.[4,8] It has been hypothesized that SCD is a much more heterogeneous condition in women, potentially attributable to the different underlying diseases, leading to differences in the associated risk factors.

Prolonged QT interval, a measure of ventricular repolarization, has been previously established as a risk factor for SCD,[9,10] and recent studies using Mendelian randomization have demonstrated that this risk factor is causal.[11] Women, on average, exhibit longer QT intervals than men in the general population once puberty is reached.[12,13] In addition, a previous study found that the increase in risk for overall cardiac death associated with prolonged QT interval was more pronounced in women.[14] Women also have higher risk of arrhythmic events than men in the setting of inherited or acquired (drug-induced) QT prolongation.[15] Based on the sex differences in QT interval in the general population and its association with overall cardiac mortality, we hypothesize that the risk of SCD associated with longer QT interval could differ by sex. Likewise, we also hypothesize that QT interval could differentially affect SCD risk depending on the underlying pathology (eg, ischemic versus non-ischemic disease).

Previous studies have shown that ≈34% of QT interval variation is heritable.[16,17] In addition, recent research indicates that ≈21% of variation can be explained by common autosomal single-nucleotide polymorphism (SNPs) found genome-wide, including SNPs in genes such as *KCNQ1, KCNH2, SCN5A,* and *NOS1AP*.[18] The top SNP from the most recent QT interval genome-wide association study was the *NOS1AP* locus SNP rs12143842, which increased QT interval by 3.50 ms per T allele ($P=1\times10^{-213}$)[19] and accounts for ≈1% of the variation in QT interval.[20] This SNP has been previously associated with increased SCD risk[21,22] and has

also been found to have stronger effect on QT interval in women than in men.[20]

In this study, we examined a large Finnish study of postmortem autopsy-confirmed SCD subjects to study the genetic association between QT interval and SCD risk. More specifically, we compared the association of the *NOS1AP* locus variant rs12143842 with SCD risk between subjects with underlying ischemic versus nonischemic disease. We also performed sex-stratified analyses within these groups to investigate any sex-specific association of the *NOS1AP* locus SNP with SCD risk. Finally, we performed Mendelian randomization to test for differences in the causal association between a previously identified causal risk factor, longer QT interval, and SCD in the setting of different underlying disease and/or between sexes.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study has institutional review board approval.

Samples

Fingesture

This study complies with the Declaration of Helsinki and has been approved by the Ethics Committee of the University of Oulu and Finland's Ministry of Social Affairs and Health. The National Supervisory Authority for Welfare and Health (which is also known as *Valvira*) and the National Institute for Health and Welfare approved the review of autopsy data by the investigators.

The Fingesture study, started in 1998, aimed to collect consecutive individuals with of out-of-hospital sudden death from a defined geographic area, Oulu University Hospital District in northern Finland. All individuals with sudden death were autopsied at the Department of Forensic Medicine, University of Oulu, Oulu, Finland. Individuals with SCD were defined as those with a witnessed sudden death within 6 hours of the onset of the symptoms or within 24 hours of the time that the individual was last seen alive in a normal state of health. Individuals with age at SCD event <30 or >80 years old were excluded from analysis.

The underlying pathologies were divided into 3 categories: (1) ischemic, (2) nonischemic, and (3) other disease. The individuals with ischemic SCD included individuals with evidence of a coronary complication, defined as a fresh intracoronary thrombus, plaque rupture or erosion, intraplaque hemorrhage, or critical coronary stenosis (>75%) in the main coronary artery. The individuals with nonischemic SCD included individuals with the following conditions: hypertrophy

caused by hypertension, valve disease, cardiomyopathy attributable to alcohol use, dilated cardiomyopathy, hypertrophic obstructive cardiomyopathy, cardiomyopathy caused by obesity, arrhythmogenic right ventricular cardiomyopathy, and primary myocardial fibrosis. Further definitions of these conditions have been previously described.[5] The "other" individuals with SCD included individuals with the following conditions: myocarditis, cardiac anomaly, and individuals with a normal autopsy (eg, individuals with a channelopathy).

Northern Finland Birth Cohort of 1966

The Ethics Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland, approved the study protocol, which followed the principles of the Declaration of Helsinki. Participation was voluntary and all participants provided their written informed consent.

The NFBC (Northern Finland Birth Cohort) study is the product of a project initiated in the 1960s to examine risk factors involved in preterm birth and intrauterine growth retardation, and the consequences of these early adverse outcomes on subsequent morbidity. The NFBC1966 cohort comprised 12 068 mothers and 12 231 children with an expected date of birth in 1966 within the province of Oulu, Finland. Our study samples consisted of DNA extracted from the blood of the offspring at their 31-year follow-up visit.

Genotyping

Samples were genotyped for rs12143842 using 5 different platforms: Illumina Infinium Global Screening Array; Affymetrix Genome-wide Human SNP Array 6.0; Agena Biosciences MassARRAY; Applied Biosystems Taqman real-time polymerase chain reaction; and Illumina TruSeq sequencing. All genotyping and sequencing were performed according to the manufacturer's instructions. Quality control was performed separately on each data set before merging. Data set and quality control information are summarized in Table S1. Overlapping samples between platforms were used to evaluate the accuracy of the genotyping (reported in Table S2). Using 1576 samples run on multiple platforms, 1957 pairwise comparisons were performed demonstrating a >99.9% concordance rate between the genotyping platforms. After exclusions, the study population included 2282 individuals with SCD and 3561 Finnish controls.

Statistical Analysis

P values for differences in the Fingesture study characteristics were calculated using a 2- sample t test for continuous variables and Pearson chi-square test for categorical variables. The genotypes for rs12143842 for all samples were merged, and logistic regression was performed using R

(version 3.3.3), with sex as the only covariate. The SCD cases were stratified by sex and underlying disease (ischemic and nonischemic) to examine the SNP associations in each group. Differences between sexes were determined by incorporating an interaction term into the regression model. Two-tailed *P* values for differences in effect sizes between ischemic and nonischemic individuals for the rs12143842 genotype were obtained by permuting the genotypes within the cases 10 000 times, thereby maintaining the overall rs12143842 association with SCD as well as the differences in ischemic prevalence between sexes, thus specifically testing the hypothesis that ischemic status modified the association. This same permutation was also used to compare the ischemic men to nonischemic women for the rs12143842 association, with the exception of using a 1-tailed *P* value to reflect the specific nature of the hypothesis tested. Two-tailed *P* values for differences in effect sizes between the underlying disease groups for the Mendelian randomization analysis were obtained from a 1-degree-of-freedom Wald test. Multidimensional scaling (MDS) using PLINK version 1.9 was used for samples run on the Global Screening Array microarray (1168 cases/761 controls) to assess potential population substructure between the Fingesture and NFBC1966 studies. MDS is a method that reduces the high number of dimensions (ie, the number of SNPs) to a smaller number of dimensions based on similarities in the data and orders these MDS dimensions (called components) on the basis of the amount of variation explained in the data.[23] Most often, population substructure accounts for the most variation within the data and is captured in the first several MDS components.

Mendelian Randomization

While association tests establish observational relationships between a trait (ie, QT interval) and an outcome (ie, SCD), they cannot establish causality. Confounding variables, variables affecting both the trait and the outcome, can result in false-positive associations. Mendelian randomization circumvents these potential confounders to establish causality by exploiting certain characteristics of SNPs: that they are (1) assigned at conception and (2) randomly distributed in the large population.[24,25] Mendelian randomization has other assumptions that must be met as well, including the absence of pleiotropy.[26] This assumption is often hard to fully meet, leading to potential bias of the results. However, recent methods have been developed to remove potentially pleiotropic SNPs to meet this assumption.

Mendelian randomization uses genetic variants as instrumental variables to test for causal relationships between a trait and an outcome. We used a multi-SNP genetic risk score association (GRSA) model to test for causality between QT interval and SCD in our stratified data sets. The SNPs used in

the model are known to be associated with the trait of interest. In this study, we used genome-wide significant SNPs from the most recent QT interval genome-wide association study.[19] The SNPs were pruned for linkage disequilibrium (LD) using the "clump" method in PLINK version 1.9, which removes any SNP within a 1-Mb window of the SNP with the lowest P value. This step is performed to remove any correlated SNPs and reduce any potential bias. The GRSA model uses 57 linkage disequilibrium–pruned SNPs to compare the association of these SNPs with the trait of interest (β_{trait}) to the association of the SNPs with SCD ($\beta_{outcome}$) using the R package "MendelianRandomization."[27] Zero-intercept inverse-weighted (IVW) linear regression is used to calculate the GRSA estimate, which is the slope of the resultant regression line, and estimates the difference in log odds of SCD risk per SD increase in QT interval. We used the HEIDI-outlier method from the "gsmr" R package to detect and remove potentially pleiotropic SNPs.[28] Finally, we used the MR-Egger Intercept test to test for the presence of pleiotropy.[29–31] P values for difference in GRSA estimates were obtained from a 1-degree-of-freedom Wald test.

Genome-wide SNP data are required for Mendelian randomization analyses and therefore only the Fingesture and NFBC1966 samples genotyped using the Infinium Global Screening Array and imputed to the National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine imputation panel using the University of Michigan imputation server[32] were used in this analysis (1168 individuals with SCD and 761 Finnish controls). Logistic regression for single SNP association tests were run using FAST version 2.4.[33] We performed several stratified analyses, including by sex and underlying disease (ischemic and nonischemic disease). There were a small number of SCD cases with other underlying disease genotyped on this array and therefore were included only in the overall analysis and sex-stratified analyses but were excluded from the underlying disease–stratified analysis and subsequent sex-stratified analyses.

Results

The SCD population is composed of a subset of the Fingesture study of Finnish SCD subjects with autopsy-confirmed assessment of underlying heart disease in whom DNA was available at the time of this study (n=2282). Controls were drawn from the NFBC1966 and are composed of 3561 Finnish individuals born in 1966. Characteristics of the Fingesture study are detailed in Table. Additional information about the different sample subgroups are provided in Table S3. To assess for potential population stratification, we ran MDS on a subset of the samples with genome-wide SNP data (1168 cases/761 controls). We assessed the top 10 MDS components, which can be used to visualize potential population substructure, for association with SCD status to test for possible confounding of our SNP association results. We ran logistic regression for SCD status, including sex and the top 10 MDS components as independent predictors in the model. Results are in Table S4. Plots for the top 10 MDS components, colored by SCD status, are found in Figure S1. MDS component 7 was associated with SCD status after multitest correction ($P<0.002$) (Table S4), indicating the potential for confounding attributable to population substructure. However, combined, the top 10 components explained only 0.9% of the variance in SCD status, suggesting likely minimal impact. This minimal impact was confirmed by sensitivity analyses (described below).

NOS1AP Locus SNP Analysis

Given the previously established relationship between QT interval and SCD risk, and with *NOS1AP* locus SNPs and SCD in other cohorts,[9,10] we first sought to assess the association between SCD and the *NOS1AP* locus SNP rs12143842. When analyzing all 2282 SCD cases and 3561 controls, the T allele of rs12143842 was significantly associated with increased SCD risk with an odds ratio (OR) of 1.14 for each copy of the QT lengthening allele (95% CI, 1.04–1.25; $P=0.005$). In sensitivity analyses, including the 10 top components from the MDS analysis in the model minimally increased the effect

Table. Fingesture Study Characteristics

Variable	All (N=2282)	Men (N=1862)	Women (N=420)	P Value*
Mean age, y (SD)	61.23 (10.71)	60.65 (10.43)	63.84 (11.56)	<0.001
Ischemic disease, N (%)	1478 (64.8)	1245 (66.9)	233 (55.5)	<0.001
Nonischemic disease, N (%)	750 (32.8)	579 (31.1)	171 (40.7)	<0.001
Other, N (%)	54 (2.4)	38 (2.0)	16 (3.8)	0.03
BMI, kg/m² (SD)	28.36 (6.61)	28.16 (6.23)	29.26 (8.10)	0.06
Heart weight, g (SD)	493.60 (129.23)	509.60 (127.83)	421.40 (109.47)	<0.001

BMI indicates body mass index; SD, standard deviation.
*P calculated for difference between men and women.

estimate (see Table S5). All SNP association results are summarized in Figure 1 and Table S6.

Ischemic versus nonischemic

To explore whether the association of rs12143842 differs by underlying disease pathology, we stratified the SCD cases into those with (1) underlying ischemic heart disease (n=1478), (2) nonischemic heart disease (n=750), and (3) other pathologies (myocarditis, cardiac anomaly, and normal autopsy; n=54). The rs12143842 T allele had the highest OR point estimate in nonischemic SCD individuals with an OR of 1.23 (95% CI, 1.07–1.39; *P*=0.003). A weaker nonsignificant association was observed in both ischemic SCD individuals (OR=1.09; 95% CI, 0.98–1.21; *P*=0.12), and those with other underlying conditions (OR=1.11; 95% CI, 0.71–1.73; *P*=0.64). A

suggestive association was observed when comparing the OR between ischemic and nonischemic SCD cases (*P*=0.12).

Men versus women

Given that QT interval is a stronger SCD risk factor in men than women, and rs12143842 has a larger effect on QT interval in women than in men,[20] we next investigated whether the association of rs12143842 on SCD risk differed between men and women. We limited sex-stratified analyses to SCD cases with underlying ischemic and nonischemic pathology and excluded those with other underlying conditions because of the small sample size of those with other conditions.

Among 1862 men with SCD and 1641 male controls, the rs12143842 QT lengthening allele was marginally associated with an increased risk of SCD (OR, 1.11; 95% CI, 0.99–1.23;
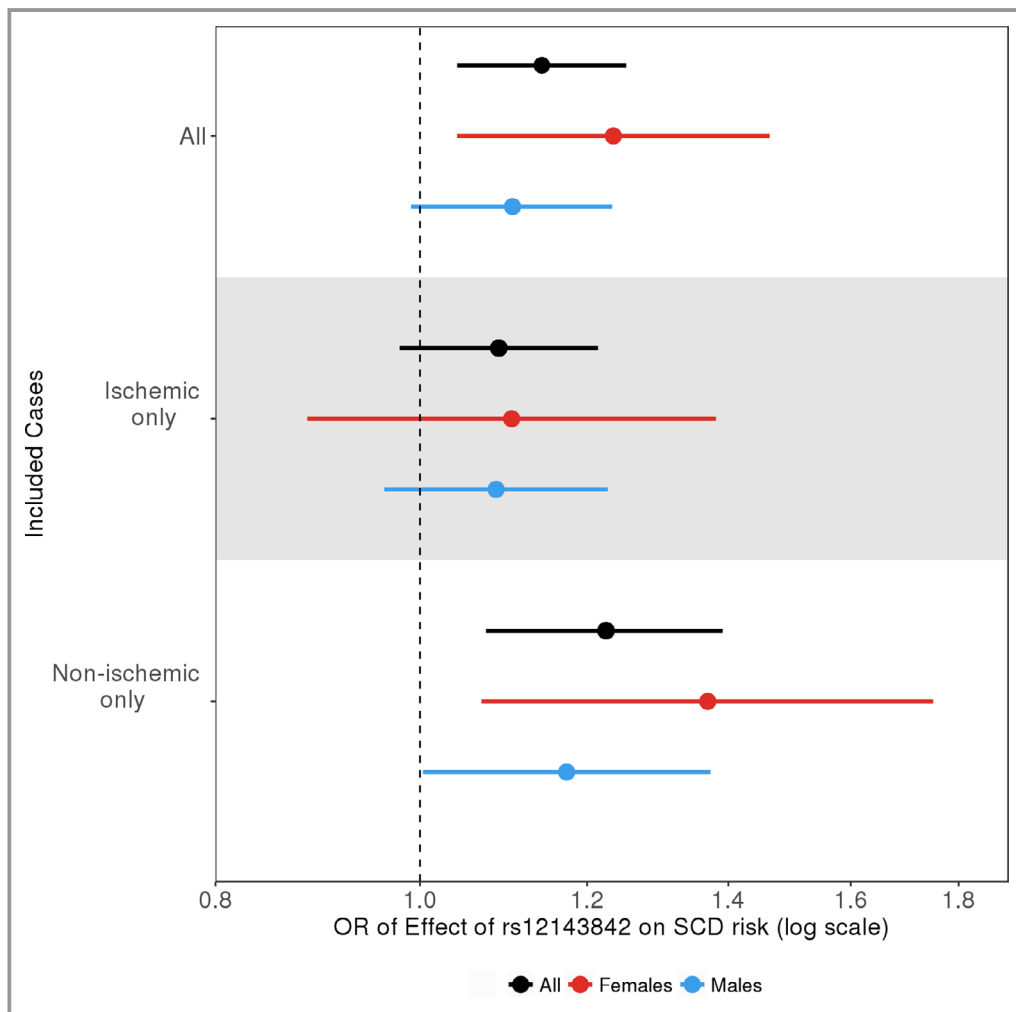
Figure 1. Forest plot of the association of rs12143842 with SCD risk. The top white panel represents the analysis including all individuals with SCD (2282 cases); the middle gray panel includes individuals with ischemic-only SCD (1478 cases); and the bottom white panel includes only individuals with nonischemic SCD (750 cases). The dots represent the OR of the rs12143842 QT lengthening allele on SCD risk, and the lines represent the 95% CIs. Both sexes (black), women only (red), and men only (blue). Additional information found in Table S6. OR indicates odds ratio; SCD, sudden cardiac death.

P=0.07). When stratified by underlying disease pathology, the association was significant among men with nonischemic SCD (579 cases/1641 controls) with an OR of 1.17 (95% CI, 1.00–1.37; P=0.045), while there was no statistically significant association in men with ischemic SCD (1245 cases/1641 controls) for SCD risk (OR=1.09; 95% CI, 0.96–1.23; P=0.18; P for difference between men with ischemic and nonischemic SCD=0.35).

Overall, among 420 female SCD cases and 1920 female controls, the rs12143842 QT lengthening allele was associated with increased SCD risk (OR of 1.24; 95% CI, 1.04–1.46; P=0.015). Similar to findings among men, a higher OR point estimate was observed in the women with nonischemic SCD (171 cases/1920 controls), with the rs12143842 T allele associated with a 1.37-fold (95% CI, 1.07–1.75; P=0.013) increased SCD risk compared with a 1.11-fold increased SCD risk (CI, 0.88–1.38; P=0.39) among women with ischemic SCD (233 cases/1920 controls; P for difference between women with ischemic and nonischemic SCD=0.20). None of the sex interaction terms was significant in the overall analysis as well as the disease-stratified analyses. However, consistent with our initial hypothesis, comparing the 2 extremes of our subgroups, nonischemic women to ischemic men, we find a significantly stronger association in the ischemic women (P=0.036).

Mendelian Randomization of QT Interval

Using Mendelian randomization approaches, we have previously established that QT interval is causally associated with SCD.[11] To investigate whether these causal associations differ on the basis of sex and underlying disease, we calculated GRSA estimates using the genome-wide significant SNPs from the most recent QT interval genome-wide association study.[19] Inverse-weighted linear regression was performed to compare the effect of the SNP on QT interval to the effect of the SNP on SCD risk in the sex-stratified and underlying disease–stratified data sets. Results are summarized in Figure 2 and Table S7. Using the MR-Egger Intercept test, we did not identify any pleiotropy biasing our results (Table S8). Finally, all effect sizes for QT interval and each SCD subgroup for the 57 SNPs used in the Mendelian randomization analyses, along with the corresponding weights ($1/SE_{SCD}^2$), are reported in Table S9.

Among all people with SCD (n=1168 cases/761 controls), a 1-SD increase in QT interval was associated with a 1.42-fold increased risk of SCD (95% CI, 0.83–2.45; P=0.20), which translates in our sample population to a 1.10-fold increased risk of SCD per 10-ms increase in QT interval (95% CI, 0.90–1.34; P=0.20). While not statistically significant, these findings are consistent with our previous work (previous findings: OR in cardiac arrest risk per SD increase in QT, 1.44;

95% CI, 1.13–1.83; P=0.018).[11] Among individuals with nonischemic SCD (507 cases/761 controls), there was a 1.96-fold increase in SCD risk per SD increase in QT (95% CI, 1.00–3.82; P=0.05). By contrast, there was no evidence of a causal association of QT interval with SCD among SCD cases with ischemic disease (611 cases/761 controls; OR=0.88; 95% CI, 0.47–1.67; P=0.70).

Similar to our findings with *NOS1AP* locus SNP rs12143842, nonischemic women with SCD had the highest OR point estimate for a causal association of QT interval with SCD (OR in SCD risk per SD increase in QT, 3.60; 95% CI, 1.22–10.59; P=0.02). Nonischemic men had a large but nonsignificant causal association estimate between QT interval and SCD (OR in SCD risk per SD increase in QT, 1.47; 95% CI, 0.64–3.39; P=0.36). Among those with underlying ischemic disease, there was no evidence for a causal relationship of QT interval with SCD for men or women (OR in SCD risk per SD increase in QT, 0.92; 95% CI, 0.41–2.05; P=0.84; and OR in SCD risk per SD increase in QT, 0.80; 95% CI 0.22–2.94; P=0.74, respectively).

Discussion

In the general population, women have longer QT intervals than men, women experience a higher rate of arrhythmias in the setting of prolonged QT interval, and prolonged QT interval is causally associated with SCD. We therefore hypothesized that women would show a greater association between genetically determined longer QT interval and SCD. Given the different etiologies between ischemic and nonischemic cardiac disease, we further hypothesized that the genetic association with longer QT interval would also differ between the different underlying diseases. Our results, while not conclusive, support both of these hypotheses. We found that rs12143842, the top QT interval-associated SNP from previous genome-wide association study,[19] was associated with SCD risk in our overall data set. We observed a larger, albeit not statistically significantly different, genetic association on SCD risk in nonischemic individuals compared with ischemic individuals. Furthermore, the women with SCD in the setting of nonischemic cardiac disease had the highest OR for the association of rs12143842 with SCD risk, with a significant difference compared with ischemic men (P=0.036). Our Mendelian randomization analyses had similar findings; nonischemic individuals showed a potential causal association between longer QT interval and SCD, and female nonischemic individuals had the highest OR point estimate for the causal association. By contrast, both the SNP association and Mendelian randomization analyses did not show evidence for a genetic (causal) association between QT interval and SCD caused by underlying ischemic disease in men or
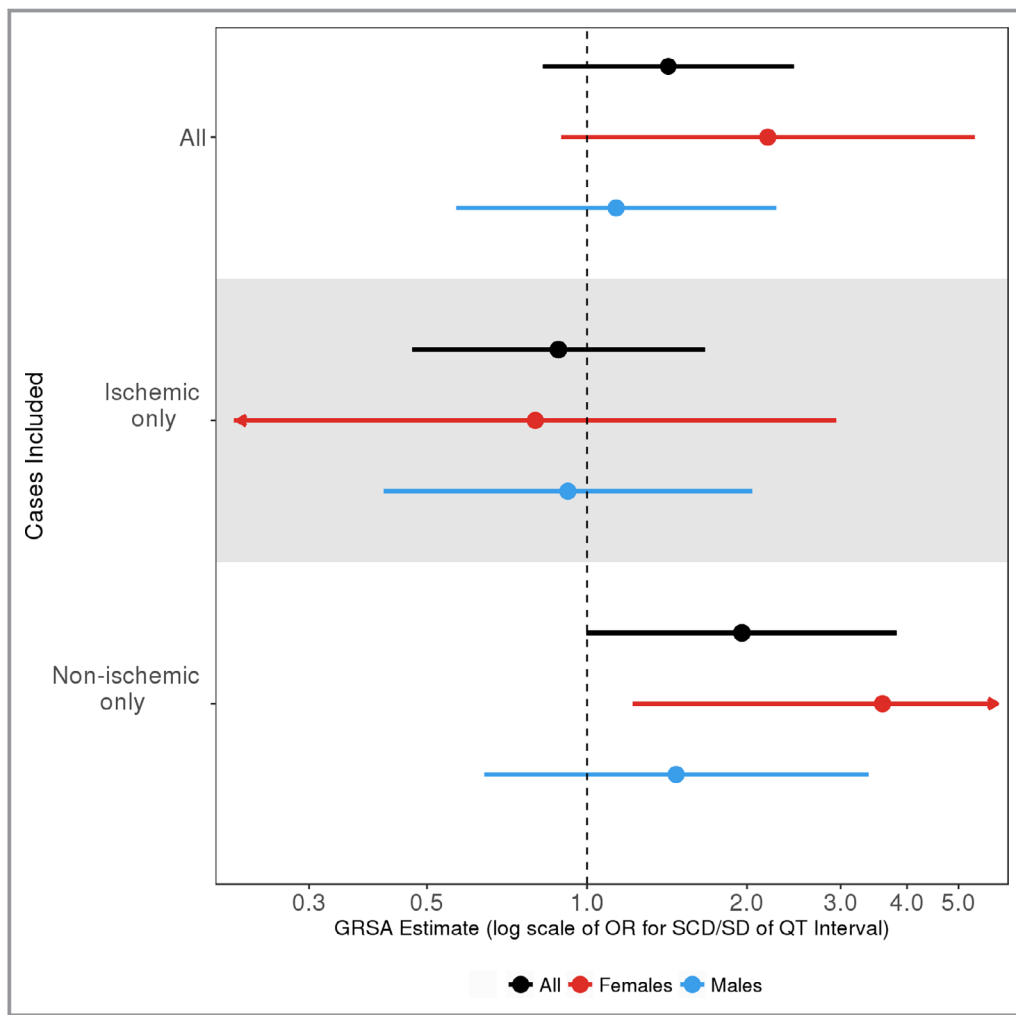
Figure 2. GRSA estimates for QT interval with SCD. The data points in the top plot represent the exponentiated GRSA estimates of QT interval on SCD (in log odds of SCD/SD of QT interval) and corresponding 95% CIs. The top white panel represents the analysis including all SCD cases used in the Mendelian randomization analysis (1168 cases); the middle gray panel includes ischemic-only SCD cases (611 cases); the bottom white panel includes only nonischemic SCD cases (507 cases). Each panel includes analyses using both sexes (black), women only (red), and men only (blue). Additional information found in Table S7. GRSA indicates genetic risk score association; OR, odds ratio; SCD, sudden cardiac death.

women. These results suggest that SCD in the setting of ischemic disease may not be strongly influenced by myocardial repolarization (QT interval) or that the effect of longer QT interval on ischemic SCD risk is masked by other risk factors exerting a larger effect. While the differences in sex- and underlying disease–stratified associations were not statistically significant, the directionality of our findings is nevertheless consistent with our underlying hypotheses that SCD risk in nonischemic individuals, particularly women with nonischemic disease, may be influenced by genetically determined QT interval.

The underlying cause(s) of the sex differences in the association between longer QT interval and SCD remains unknown; however, sex hormones may play a role. Studies have previously established that testosterone and progesterone shorten the QT interval, while estrogen lengthens the QT interval.[34,35] While the underlying mechanism is unknown, our findings support the hypothesis that nonischemic individuals are more susceptible to the effects of longer QT interval on developing SCD. Given that women already have underlying lengthened QT attributable to sex hormones, the addition of QT lengthening genetic susceptibility (ie, the T allele of the *NOS1AP* SNP rs12143842) may result in the higher observed risk of SCD in women with nonischemic disease.

While our study is consistent with the hypothesis that differences in SCD risk factors exist on the basis of both underlying disease and sex, several limitations should be noted. First, many of our analyses did not meet traditional

statistical significance cutoffs, though we note that the directionality of the results is entirely consistent with our original hypotheses. The study is underpowered to detect interactions, and thus, additional samples are necessary to confirm our results. Our findings in the subgroup analyses also require additional replication. Second, there is likely additional phenotypic heterogeneity within the underlying disease subgroups. The nonischemic group, as noted in the supplementary methods, consists of 8 different cardiac conditions. It is possible these different conditions, while similar in nature, may differ in their relationship between QT interval and SCD risk. Additional samples are needed to further stratify the nonischemic group to investigate whether a particular condition is driving the association. Third, while our MDS components indicated potential population sub-structure within a subset of samples, when we included the components as covariates in our analysis, the association was actually stronger. Therefore, not adjusting our main analysis for population substructure is likely resulting in a downward bias of the true association. Fourth, the NFBC1966 cohort used for our controls consisted of relatively young individuals (31 years old). Given that the mean age of our SCD cohort was 60 years, it is likely some of our "controls" will go on to have an SCD event later in life, and by not excluding these individuals, we bias our estimates toward the null. Fifth, the Finnish population is quite homogenous, and therefore our findings may not be applicable to other populations, including other Europeans. Finally, the highest OR point estimates were seen in women, and as women on average have lower rates of SCD, we have the least power to detect differences within this group. Nevertheless, our findings that women with SCD with nonischemic disease had the highest OR point estimates for the association between longer QT interval and SCD risk were consistent among the various analyses performed, including both SNP association tests and Mendelian ran-domization. The directionality of our findings is consistent with our original hypothesis, which stated that the effect of longer QT interval will differ by underlying disease pathology and would be stronger in women than in men.

In conclusion, we observed a significant genetic associa-tion in individuals with nonischemic SCD, as well as a potentially causal association, between longer QT interval and SCD risk. The highest OR point estimate was observed in women with nonischemic SCD, with the effect significantly higher than that observed in men with ischemic SCD. Indeed, individuals with SCD with underlying ischemic disease did not exhibit a significant genetic association or a causal associ-ation between longer QT interval and SCD, regardless of sex. In sum, our findings are consistent with a model in which SCD risk factors, particularly longer QT interval, may differ between sex and underlying disease etiology.

Disclosures

None.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.

2. Yousuf O, Chrispin J, Tomaselli GF, Berger RD. Clinical management and prevention of sudden cardiac death. *Circ Res*. 2015;116:2020–2040.

3. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, Stampfer MJ, Manson JE. Prospective study of sudden cardiac death among women in the United States. *Circulation*. 2003;107:2096–2101.

4. Kannel WB, Wilson PWF, D'Agostino RB, Cobb J. Sudden coronary death in women. *Am Heart J*. 1998;136:205–212.

5. Haukilahti MAE, Holmström L, Vähätalo J, Kenttä T, Tikkanen J, Pakanen L, Kortelainen ML, Perkiömäki J, Huikuri H, Myerburg RJ, Junttila MJ. Sudden cardiac death in women. *Circulation*. 2019;139:1012–1021.

6. Albert CM, McGovern BA, Newell JB, Ruskin JN. Sex differences in cardiac arrest survivors. *Circulation*. 1996;93:1170–1176.

7. Chugh SS, Uy-Evanado A, Teodorescu C, Reinier K, Mariani R, Gunson K, Jui J. Women have a lower prevalence of structural heart disease as a precursor to

sudden cardiac arrest: the Ore-SUDS (Oregon Sudden Unexpected Death Study). *J Am Coll Cardiol.* 2009;54:2006–2011.

8. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJA, Houben LG, Wellens HJ. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol.* 1997;30:1500–1505.

9. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation.* 1991;83:1888–1894.

10. Straus SMJM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol.* 2006;47:362–367.

11. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Müller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, Junttila MJ, Goyette P, Pulit SL, Pazoki R, Tanck MW, Blom MT, Zhao X, Havulinna AS, Jabbari R, Glinge C, Tragante V, Escher SA, Chakravarti A, Ehret G, Coresh J, Li M, Prineas RJ, Franco OH, Kwok PY, Lumley T, Dumas F, McKnight B, Rotter JI, Lemaitre RN, Heckbert SR, O'Donnell CJ, Hwang SJ, Tardif JC, VanDenburgh M, Uitterlinden AG, Hofman A, Stricker BHC, de Bakker PIW, Franks PW, Jansson JH, Asselbergs FW, Halushka MK, Maleszewski JJ, Tfelt-Hansen J, Engstrøm T, Salomaa V, Virmani R, Kolodgie F, Wilde AAM, Tan HL, Bezzina CR, Eijgelsheim M, Rioux JD, Jouven X, Kääb S, Psaty BM, Siscovick DS, Arking DE, Sotoodehnia N. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. *Eur Heart J.* 2018;39:3961–3969.

12. Pfeufer A, Jalilzadeh S, Perz S, Mueller JC, Hinterseer M, Illig T, Akyol M, Huth C, Schöpfer-Wendels A, Kuch B, Steinbeck G, Holle R, Näbauer M, Wichmann HE, Meitinger T, Kääb S. Common variants in myocardial ion channel genes modify the QT interval in the general population. *Circ Res.* 2005;96:693–701.

13. Vicente J, Johannesen L, Galeotti L, Strauss DG. Mechanisms of sex and age differences in ventricular repolarization in humans. *Am Heart J.* 2014;168:749–756.e3.

14. de Bruyne M, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 1999;20:278–284.

15. Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, McNitt S, Polonsky S, Robinson JL, Zareba W, Ackerman MJ, Benhorin J, Kaufman ES, Platonov PG, Shimizu W, Towbin JA, Vincent GM, Wilde AA, Goldenberg I. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. *Heart Rhythm.* 2011;8:1537–1543.

16. Hong Y, Rautaharju P, Hopkins P, Arnett D, Djoussé L, Pankow J, Sholinsky P, Rao DC, Province MA. Familial aggregation of QT-interval variability in a general population: results from the NHLBI Family Heart Study. *Clin Genet.* 2001;59:171–177.

17. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, D'Agostino RB, O'Donnell CJ. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: the Framingham Heart Study. *Heart Rhythm.* 2005;2:277–284.

18. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, de Andrade M, Feenstra B, Feingold E, Hayes MG, Hill WG, Landi MT, Alonso A, Lettre G, Lin P, Ling H, Lowe W, Mathias RA, Melbye M, Pugh E, Cornelis MC, Weir BS, Goddard ME, Visscher PM. Genome partitioning of genetic variation for complex traits using common SNPs. *Nat Genet.* 2011;43:519–525.

19. Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, Sotoodehnia N, Rossin EJ, Morley M, Wang X, Johnson AD, Lundby A, Gudbjartsson DF, Noseworthy PA, Eijgelsheim M, Bradford Y, Tarasov KV, Dörr M, Müller-Nurasyid M, Lahtinen AM, Nolte IM, Smith AV, Bis JC, Isaacs A, Newhouse SJ, Evans DS, Post WS, Waggott D, Lyytikäinen LP, Hicks AA, Eisele L, Ellinghaus D, Hayward C, Navarro P, Ulivi S, Tanaka T, Tester DJ, Chatel S, Gustafsson S, Kumari M, Morris RW, Naluai ÅT, Padmanabhan S, Kluttig A, Strohmer B, Panayiotou AG, Torres M, Knoflach M, Hubacek JA, Slowikowski K, Raychaudhuri S, Kumar RD, Harris TB, Launer LJ, Shuldiner AR, Alonso A, Bader JS, Ehret G, Huang H, Kao WH, Strait JB, Macfarlane PW, Brown M, Caulfield MJ, Samani NJ, Kronenberg F, Willeit J; CARe Consortium; COGENT Consortium; Smith JG, Greiser KH, Meyer Zu Schwabedissen H, Werdan K, Carella M, Zelante L, Heckbert SR, Psaty BM, Rotter JI, Kolcic I, Polašek O, Wright AF, Griffin M, Daly MJ; DCCT/EDIC, Arnar DO, Hólm H, Thorsteinsdottir U; eMERGE Consortium, Denny JC, Roden DM, Zuvich RL, Emilsson V, Plump AS, Larson MG, O'Donnell CJ, Yin X, Bobbo M, D'Adamo AP, Iorio A, Sinagra G, Carracedo A, Cummings SR, Nalls MA, Jula A, Kontula KK, Marjamaa A, Oikarinen L, Perola M, Porthan K, Erbel R, Hoffmann P, Jöckel KH, Kälsch H, Nöthen MM; HRGEN Consortium, den Hoed M, Loos RJ, Thelle DS, Gieger C, Meitinger T, Perz S, Peters A, Prucha H, Sinner MF, Waldenberger M, de Boer RA, Franke L, van der Vleuten PA, Beckmann BM, Martens E, Bardai A, Hofman N, Wilde AA, Behr ER, Dalageorgou C, Giudicessi JR, Medeiros-Domingo A, Barc J, Kyndt F, Probst V, Ghidoni A, Insolia R, Hamilton RM, Scherer SW, Brandimarto J, Margulies K, Moravec CE, del Greco MF, Fuchsberger C,

O'Connell JR, Lee WK, Watt GC, Campbell H, Wild SH, El Mokhtari NE, Frey N, Asselbergs FW, Mateo Leach I, Navis G, van den Berg MP, van Veldhuisen DJ, Kellis M, Krijthe BP, Franco OH, Hofman A, Kors JA, Uitterlinden AG, Witteman JC, Kedenko L, Lamina C, Oostra BA, Abecasis GR, Lakatta EG, Mulas A, Orrú M, Schlessinger D, Uda M, Markus MR, Völker U, Snieder H, Spector TD, Ärnlöv J, Lind L, Sundström J, Syvänen AC, Kivimaki M, Kähönen M, Mononen N, Raitakari OT, Viikari JS, Adamkova V, Kiechl S, Brion M, Nicolaides AN, Paulweber B, Haerting J, Dominiczak AF, Nyberg F, Whincup PH, Hingorani AD, Schott JJ, Bezzina CR, Ingelsson E, Ferrucci L, Gasparini P, Wilson JF, Rudan I, Franke A, Mühleisen TW, Pramstaller PP, Lehtimäki TJ, Paterson AD, Parsa A, Liu Y, van Duijn CM, Siscovick DS, Gudnason V, Jamshidi Y, Salomaa V, Felix SB, Sanna S, Ritchie MD, Stricker BH, Stefansson K, Boyer LA, Cappola TP, Olsen JV, Lage K, Schwartz PJ, Kääb S, Chakravarti A, Ackerman MJ, Pfeufer A, de Bakker PI, Newton-Cheh C. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat Genet.* 2014;46:826–836.

20. Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C, Ehret GB, Orrú M, Pattaro C, Köttgen A, Perz S, Usala G, Barbalic M, Li M, Pütz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Mühleisen TW, Dei M, Happle C, Möhlenkamp S, Crisponi L, Erbel R, Jöckel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Müller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kääb S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet.* 2009;41:407–414.

21. Eijgelsheim M, Newton-Cheh C, Aarnoudse ALHJ, van Noord C, Witteman JCM, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in NOS1AP is associated with sudden cardiac death: evidence from the Rotterdam Study. *Hum Mol Genet.* 2009;18:4213–4218.

22. Arking DE, Pfeufer A, Post W, Kao WHL, Newton-Cheh C, Ikeda M, West K, Kashuk C, Akyol M, Perz S, Jalilzadeh S, Illig T, Gieger C, Guo CY, Larson MG, Wichmann HE, Marbán E, O'Donnell CJ, Hirschhorn JN, Kääb S, Spooner PM, Meitinger T, Chakravarti A. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet.* 2006;38:644–651.

23. Tian C, Gregersen PK, Seldin MF. Accounting for ancestry: population substructure and genome-wide association studies. *Hum Mol Genet.* 2008;17:R143–R150.

24. Brion M-JA, Benyamin B, Visscher PM, Smith GD. Beyond the single SNP: emerging developments in Mendelian randomization in the "Omics" era. *Curr Epidemiol Rep.* 2014;1:228–236.

25. Swerdlow DI, Kuchenbaecker KB, Shah S, Sofat R, Holmes MV, White J, Mindell JS, Kivimaki M, Brunner EJ, Whittaker JC, Casas JP. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. *Int J Epidemiol.* 2016;45:1600–1616.

26. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. *Int J Epidemiol.* 2013;42:1134–1144.

27. Yavorska OA, Burgess S. Package 'MendelianRandomization'. 2018.

28. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, Robinson MR, McGrath JJ, Visscher PM, Wray NR, Yang J. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun.* 2018;9:224.

29. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015;44:512–525.

30. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan NA, Thompson JR. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I2 statistic. *Int J Epidemiol.* 2016;45:1961–1974.

31. Burgess S, Foley CN, Zuber V. Inferring causal relationships between risk factors and outcomes from genome-wide association study data. *Annu Rev Genomics Hum Genet.* 2018;19:303–327.

32. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. *Nat Genet.* 2016;48:1284–1287.

33. Chanda P, Huang H, Arking DE, Bader JS. Fast association tests for genes with FAST. *PLoS One.* 2013;8:e68585.

34. Zhang Y, Ouyang P, Post WS, Dalal D, Vaidya D, Blasco-Colmenares E, Soliman EZ, Tomaselli GF, Guallar E. Sex-steroid hormones and electrocardiographic QT-interval duration: findings from the third National Health and Nutrition Examination Survey and the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol.* 2011;174:403–411.

35. Nakagawa M, Ooie T, Takahashi N, Taniguchi Y, Anan F, Yonemochi H, Saikawa T. Influence of menstrual cycle on QT interval dynamics. *Pacing Clin Electrophysiol.* 2006;29:607–613.

SUPPLEMENTAL MATERIAL

Table S1. Genotyping Platform Sample Characteristics

Genotyping platform	Illumina Infinium Global Screening Array (GSA)	Affymetrix Genome-wide Human SNP Array 6.0	Agena Biosciences MassARRAY	AB Taqman	Illumina Sequencing
N, number of total cases	1168	358	574	572	825
N, number of total controls	761	NA	422	2175	563
N, number of independent cases	1168	315	122	496	181
N, number of independent controls	761	NA	251	2140	408
Quality control critieria	Sample and SNP call rate (<95%); sex check; duplicate removal; cryptic relatedeness; genetic outlier removal using PCA	Sample and SNP call rate (<95%); sex check; duplicate removal; cryptic relatedeness; genetic outlier removal using PCA	Sample and SNP call rate (<95%)	NA	Minimum SNP read depth (10x); Sample and SNP call rate (<95%); sex check; duplicate removal; cryptic relatedeness; genetic outlier removal using PCA
Sex, number of women among independent cases	218	50	30	91	31
Sex, number of women among independent controls	407	NA	145	1140	228
Age, mean age at SCD event	60.1	62.8	59.8	64.3	58
N, number of ischemic SCD cases	610	310	44	427	87
N, number of non-ischemic SCD cases	557	5	78	69	94
Number of non-matching alleles between overlap samples	0	0	1*	0	1*

*Same sample; removed from both datasets

AB=Applied Biosystems; SNP=single nucleotide polymorphism; PCA=prinicpal component analysis; SCD=sudden cardiac death

Table S2. Overlapping samples between genotyping platforms

Platform	GSA array	Affy array	MassARRAY	Sequencing	Taqman
GSA array	-	43	708	454	111
Affy array	43	-	230	347	9
MassARRAY	708	230	-	55	0
Sequencing	454	347	55	-	0
Taqman	111	9	0	0	-

Table S3. Sample subgroup characteristics

Subgroup	N	Mean Age (SD)	N, Female	*NOS1AP* SNP T Allele Frequency
All Fingesture cases	2,282	61.23 (10.71)	420	0.264
Female Fingesture cases	420	63.84 (11.56)	420	0.285
Male Fingesture cases	1,862	60.65 (10.43)	0	0.259
Ischemic Fingesture cases	1,478	64.10 (9.70)	233	0.258
Non-ischemic Fingesture cases	750	56.22 (10.48)	171	0.276
Fingesture cases, age 30-55	658	48.12 (5.99)	93	0.270
Fingesture cases, age 56-85	1,604	66.70 (6.84)	322	0.262
All NFBC1966 controls	3,561	31 (0)	1,920	0.242
Female NFBC1966 controls	1,920	31 (0)	1,920	0.244
Male NFBC1966 controls	1,641	31 (0)	0	0.240

SD=standard deviation; SNP=single nucleotide polymorphism

Table S4. Multi-dimensional scaling (MDS) logistic regression results for SCD status

Variable	Beta	SE	*P*
Sex	-1.61	0.105	<0.001
MDS Component 1	-0.296	0.328	0.36
MDS Component 2	-0.231	0.288	0.42
MDS Component 3	0.477	0.189	0.011
MDS Component 4	-0.265	0.292	0.37
MDS Component 5	0.099	0.269	0.71
MDS Component 6	0.147	0.245	0.55
MDS Component 7	0.316	0.102	0.002
MDS Component 8	0.009	0.210	0.97
MDS Component 9	-0.002	0.197	0.99
MDS Component 10	0.001	0.194	0.99

*Components were re-scaled by multiplying by 100 before regression to avoid numerical errors in R

MDS=multi-dimensional scaling; SE=standard error

Table S5. Multi-dimensional scaling (MDS) logistic regression results for rs12143842 and SCD status

Variables used in model	Beta	SE	*P*	Variance Explained
Sex	0.211	0.083	0.011	0.101
Sex + MDS Components 1-10	0.227	0.084	0.007	0.108

SCD=sudden cardiac death; SE=standard error; MDS=multi-dimensional scaling

Table S6. rs12143842 SNP association results for SCD status

	All				
Dataset	**cases/controls**	**Beta**	**SE**	***P***	***P* for ischemic/ non-ischemic difference**
All cases/population controls	2282/3561	0.133	0.047	0.005	
ischemic cases/population controls	1478/3561	0.086	0.055	0.11	0.12
non-ischemic cases/population controls	750/3561	0.203	0.067	0.003	

	Males only				
Dataset	**cases/controls**	**Beta**	**SE**	***P***	***P* for ischemic/ non-ischemic difference**
All cases/population controls	1862/1641	0.101	0.056	0.07	
ischemic cases/population controls	1245/1641	0.083	0.062	0.18	0.35
non-ischemic cases/population controls	579/1641	0.160	0.080	0.045	

	Females only					
Dataset	**cases/controls**	**Beta**	**SE**	***P***	***P* for ischemic/ non-ischemic difference**	**P-value for interaction term (Sex*SNP)**
All cases/population controls	420/1920	0.211	0.087	0.015		0.29
ischemic cases/population controls	233/1920	0.100	0.114	0.39	0.20	0.89
non-ischemic cases/population controls	171/1920	0.314	0.126	0.013		0.30

SNP=single nucleotide polymorphism; SCD=sudden cardiac death; SE=standard error

Table S7. Mendelian randomization of QT interval and SCD results using IVW

	All				
Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	P for ishemic/non-ischemic difference
All cases/population controls	1168/761	57	0.352 [-0.191, 0.895]	0.20	
ischemic cases/population controls	611/761	57	-0.124 [-0.757, 0.510]	0.70	0.09
non-ischemic cases/population controls	507/761	57	0.671 [-0.003, 1.340]	0.05	

	Males only				
Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	P for ishemic/non-ischemic difference
All cases/population controls	950/354	57	0.126 [-0.567, 0.820]	0.72	
ischemic cases/population controls	528/354	57	-0.083 [-0.881,0.716]	0.84	0.43
non-ischemic cases/population controls	387/354	57	0.386 [-0.445,1.220]	0.36	

	Females only					
Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	P for ishemic/non-ischemic difference	P for male/female difference
All cases/population controls	218/407	57	0.783 [-0.112, 1.680]	0.09		0.26
ischemic cases/population controls	83/407	57	-0.224 [-1.530, 1.080]	0.74	0.08	0.86
non-ischemic cases/population controls	120/407	57	1.28 [0.202, 2.360]	0.020		0.20

IVW=inverse weighted; SCD=sudden cardiac death; SNP=single nucleotide polymorphism; CI=confidence interval; SE=standard error

Table S8. Sensitivity analysis using MR-Egger Intercept Test for Pleiotropy for SCD and QT Interval

Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	Intercept (SE)	P for Intercept
			All			
All cases/population controls	1168/761	57	0.465 [-0.478, 1.408]	0.33	-0.006 (0.022)	0.77
ischemic cases/population controls	611/761	57	-0.140 [0.563, -1.244]	0.80	0.001 (0.025)	0.97
non-ischemic cases/population controls	507/761	57	0.915 [-0.253, 2.083]	0.13	-0.014 (0.027)	0.62

Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	Intercept (SE)	P for Intercept
			Males only			
All cases/population controls	950/354	57	0.349 [-0.851, 1.550]	0.568	-0.012 (0.028)	0.65
ischemic cases/population controls	528/354	57	0.346 [-1.036, 1.729]	0.62	-0.024 (0.032)	0.46
non-ischemic cases/population controls	387/354	57	0.393 [-0.066, 0.065]	0.59	0.00 (0.033)	0.99

Dataset	cases/controls	SNPs included	GRSA Estimate [95% CI]	P	Intercept (SE)	P for Intercept
			Females only			
All cases/population controls	218/407	57	0.686 [-0.866, 2.239]	0.39	0.005 (0.036)	0.88
ischemic cases/population controls	83/407	57	-1.377 [-3.577, 0.823]	0.22	0.066 (0.052)	0.20
non-ischemic cases/population controls	120/407	57	1.728 [-0.141, 3.598]	0.07	-0.025 (0.043)	0.56

MR=Mendelian randomization; SCD=sudden cardiac death; SNPs=single nucleotide polymorphisms; CI=confidence interval; SE=standard error

Table S9. Effect sizes and Weights for Mendelian Randomization analyses for QT interval and SCD

SNP	QT Effect	All SCD Effect	All Weights (1/SE²)	All Male SCD Effect	All Male Weights (1/SE²)	All Female SCD Effect	All Female Weights (1/SE²)
rs10076361	-0.027	0.006	130.109	0.025	84.870	0.003	43.161
rs10172414	-0.020	-0.010	187.295	-0.008	120.477	-0.013	64.815
rs1042391	0.021	0.103	193.841	0.080	121.468	0.150	69.711
rs10919070	0.056	0.069	73.160	-0.187	40.657	0.450	24.449
rs11153730	-0.055	0.073	193.383	0.055	123.136	0.098	67.930
rs11779860	0.020	0.164	180.788	0.180	117.350	0.152	61.029
rs12061601	0.046	0.033	85.910	-0.042	54.091	0.127	28.854
rs12079745	-0.045	0.220	48.944	0.324	31.736	0.005	14.557
rs12143842	0.117	0.228	140.454	0.226	87.913	0.247	51.589
rs12210733	-0.068	0.067	25.526	0.206	15.037	-0.210	8.423
rs12567315	0.094	0.074	166.605	0.051	107.161	0.113	59.333
rs12567682	-0.025	0.051	95.582	0.031	58.049	0.043	36.288
rs13228494	-0.052	-0.038	159.676	-0.123	101.968	0.104	53.846
rs1549607	-0.058	0.030	152.376	-0.017	101.777	0.135	50.495
rs1634800	-0.033	-0.078	188.581	-0.184	118.179	0.105	65.787
rs164594	0.026	0.005	93.953	-0.040	59.686	0.057	31.742
rs16857031	-0.079	-0.059	53.086	0.064	35.250	-0.303	19.505
rs17457880	-0.065	-0.333	15.247	-0.509	11.313	0.001	4.614
rs17460657	0.167	-0.010	42.985	0.008	28.818	-0.058	14.173
rs17763769	0.030	-0.122	106.289	-0.070	67.757	-0.195	35.540
rs1805126	0.035	0.068	189.097	0.032	122.319	0.139	63.743
rs1983546	0.027	-0.094	192.978	-0.164	121.337	0.005	68.129
rs2041678	0.021	-0.053	119.679	-0.140	73.497	0.100	42.161
rs2074238	-0.165	-0.079	40.486	0.009	24.750	-0.256	13.934
rs2193565	0.057	-0.297	40.306	-0.400	25.016	-0.093	13.182
rs2273042	0.031	-0.162	81.142	-0.116	53.721	-0.263	24.930
rs2273905	0.023	-0.002	126.820	-0.103	81.202	0.217	44.295
rs236586	-0.021	-0.034	199.301	-0.070	125.354	0.027	71.810
rs246185	-0.024	0.045	161.935	0.010	102.011	0.099	57.894
SNP=single nucleotide polymorphism; SCD=sudden cardiac death; SE=stardard error							

SNP	All Isch SCD Effect	All Isch Weights (1/SE²)	Isch Male Effect	Isch Male Weights (1/SE²)	Isch Female SCD Effect	Isch Female Weights (1/SE²)
rs10076361	0.110	94.719	0.099	71.690	0.272	20.758
rs10172414	-0.034	132.857	-0.049	99.278	0.017	29.506
rs1042391	0.062	134.301	0.083	98.474	-0.028	30.847
rs10919070	0.004	52.179	-0.262	35.181	0.798	8.140
rs11153730	0.089	133.951	0.069	99.207	0.110	30.101
rs11779860	0.212	127.704	0.206	95.784	0.379	27.231
rs12061601	-0.061	62.997	-0.201	45.743	0.245	11.502
rs12079745	0.140	33.344	0.217	25.087	-0.332	5.226
rs12143842	0.158	96.164	0.216	71.446	0.081	20.766
rs12210733	0.124	18.325	0.256	12.885	-0.356	3.321
rs12567315	0.038	115.414	0.040	86.052	0.071	26.943
rs12567682	0.106	64.934	0.107	46.963	0.034	16.073
rs13228494	0.049	111.920	-0.103	83.971	0.545	19.459
rs1549607	0.029	106.606	-0.025	81.158	0.251	23.538
rs1634800	-0.141	134.346	-0.213	98.300	0.031	30.020
rs164594	-0.118	66.758	-0.101	48.765	-0.254	16.184
rs16857031	0.021	36.331	0.143	27.833	-0.339	9.101
rs17457880	-0.337	11.178	-0.475	8.980	-0.079	1.933
rs17460657	-0.085	30.128	-0.028	23.022	-0.245	7.125
rs17763769	-0.146	72.115	-0.112	53.815	-0.243	14.560
rs1805126	0.062	131.808	0.047	97.173	0.124	29.219
rs1983546	-0.065	132.778	-0.180	96.892	0.228	28.162
rs2041678	-0.084	85.452	-0.186	61.637	0.126	18.698
rs2074238	-0.120	26.976	-0.179	19.435	0.043	6.738
rs2193565	-0.438	28.528	-0.445	20.532	-0.499	7.313
rs2273042	-0.241	51.906	-0.246	39.233	-0.264	10.839
rs2273905	0.086	87.818	-0.026	65.630	0.460	19.474
rs236586	-0.068	136.368	-0.063	99.555	-0.090	32.416
rs246185	0.099	113.944	0.097	85.575	0.112	25.071

SNP=single nucleotide polymorphism; Isch=ischemic; SCD=sudden cardiac death; SE=stardard error

SNP	All Isch SCD Effect	All Isch Weights (1/SE²)	Isch Male Effect	Isch Male Weights (1/SE²)	Isch Female SCD Effect	Isch Female Weights (1/SE²)
rs10076361	0.110	94.719	0.099	71.690	0.272	20.758
rs10172414	-0.034	132.857	-0.049	99.278	0.017	29.506
rs1042391	0.062	134.301	0.083	98.474	-0.028	30.847
rs10919070	0.004	52.179	-0.262	35.181	0.798	8.140
rs11153730	0.089	133.951	0.069	99.207	0.110	30.101
rs11779860	0.212	127.704	0.206	95.784	0.379	27.231
rs12061601	-0.061	62.997	-0.201	45.743	0.245	11.502
rs12079745	0.140	33.344	0.217	25.087	-0.332	5.226
rs12143842	0.158	96.164	0.216	71.446	0.081	20.766
rs12210733	0.124	18.325	0.256	12.885	-0.356	3.321
rs12567315	0.038	115.414	0.040	86.052	0.071	26.943
rs12567682	0.106	64.934	0.107	46.963	0.034	16.073
rs13228494	0.049	111.920	-0.103	83.971	0.545	19.459
rs1549607	0.029	106.606	-0.025	81.158	0.251	23.538
rs1634800	-0.141	134.346	-0.213	98.300	0.031	30.020
rs164594	-0.118	66.758	-0.101	48.765	-0.254	16.184
rs16857031	0.021	36.331	0.143	27.833	-0.339	9.101
rs17457880	-0.337	11.178	-0.475	8.980	-0.079	1.933
rs17460657	-0.085	30.128	-0.028	23.022	-0.245	7.125
rs17763769	-0.146	72.115	-0.112	53.815	-0.243	14.560
rs1805126	0.062	131.808	0.047	97.173	0.124	29.219
rs1983546	-0.065	132.778	-0.180	96.892	0.228	28.162
rs2041678	-0.084	85.452	-0.186	61.637	0.126	18.698
rs2074238	-0.120	26.976	-0.179	19.435	0.043	6.738
rs2193565	-0.438	28.528	-0.445	20.532	-0.499	7.313
rs2273042	-0.241	51.906	-0.246	39.233	-0.264	10.839
rs2273905	0.086	87.818	-0.026	65.630	0.460	19.474
rs236586	-0.068	136.368	-0.063	99.555	-0.090	32.416
rs246185	0.099	113.944	0.097	85.575	0.112	25.071

SNP=single nucleotide polymorphism; Isch=ischemic; SCD=sudden cardiac death; SE=stardard error

SNP	All Isch SCD Effect	All Isch Weights (1/SE²)	Isch Male Effect	Isch Male Weights (1/SE²)	Isch Female SCD Effect	Isch Female Weights (1/SE²)
rs2579344	0.058	58.353	0.058	40.951	0.172	14.871
rs3026445	-0.147	131.941	-0.076	99.760	-0.408	27.889
rs347272	-0.008	67.510	-0.050	50.955	0.053	15.594
rs3857067	0.053	129.041	0.055	96.002	0.009	28.675
rs3902035	0.050	110.374	0.095	79.902	0.009	27.106
rs3922843	0.075	88.053	0.255	62.157	-0.533	16.489
rs4246215	-0.050	126.183	-0.051	93.648	-0.203	27.259
rs457162	-0.325	28.457	-0.493	17.165	0.040	7.445
rs4656345	0.013	20.205	-0.261	14.861	0.637	6.513
rs4784934	0.071	95.191	0.038	74.395	0.163	19.497
rs545833	-0.011	120.543	-0.087	91.194	0.093	25.971
rs6599250	-0.067	133.554	-0.066	98.513	-0.045	30.695
rs6669543	0.010	80.105	0.010	59.857	0.009	18.246
rs6947240	0.115	75.360	0.063	57.472	0.283	16.036
rs7122937	0.007	112.445	-0.056	83.241	0.123	26.061
rs7174839	0.080	135.260	0.020	100.253	0.226	29.780
rs7545047	-0.205	16.294	-0.208	11.564	-0.452	3.413
rs7561149	-0.069	133.986	-0.067	100.955	-0.094	29.372
rs7681503	-0.055	124.056	-0.049	93.211	-0.158	26.042
rs8049607	0.045	121.924	0.047	89.748	0.112	27.485
rs8063949	0.164	79.329	0.180	58.389	0.148	18.412
rs808963	0.031	65.671	-0.005	49.096	0.208	12.816
rs846111	-0.262	81.702	-0.285	61.948	-0.332	16.664
rs938291	-0.104	128.050	-0.122	96.253	-0.036	27.872
rs946267	0.251	54.954	0.421	37.966	-0.240	10.655
rs9851710	0.000	113.979	0.004	84.689	0.114	24.262
rs9856587	0.114	61.452	0.130	46.210	0.066	13.706
rs9920	0.115	38.388	0.022	28.532	0.364	6.999

SNP=single nucleotide polymorphism; Isch=ischemic; SCD=sudden cardiac death; SE=stardard error

| SNP	All Non-isch SCD Effect	All Non-isch Weights (1/SE²)	Non-isch Male SCD Effect	Non-isch Male Weights (1/SE²)	Non-isch Female SCD Effect	Non-isch Female Weights (1/SE²)
rs10076361	-0.098	90.257	-0.063	57.443	-0.286	25.634
rs10172414	0.020	136.203	0.055	83.292	-0.065	42.463
rs1042391	0.133	141.498	0.101	85.283	0.269	45.903
rs10919070	0.068	49.533	-0.083	26.962	0.467	14.951
rs11153730	0.047	140.675	0.065	86.376	0.106	44.844
rs11779860	0.109	128.597	0.184	80.541	-0.084	38.553
rs12061601	0.138	59.715	0.152	36.801	0.058	20.301
rs12079745	0.352	37.873	0.462	23.863	0.192	10.587
rs12143842	0.284	103.164	0.289	61.363	0.309	34.465
rs12210733	0.065	18.246	0.188	10.540	0.032	6.406
rs12567315	0.089	122.188	0.057	75.614	0.167	39.208
rs12567682	-0.023	71.968	-0.055	41.424	0.003	24.229
rs13228494	-0.136	117.024	-0.134	71.885	-0.133	37.596
rs1549607	0.025	110.837	-0.011	70.733	0.101	32.845
rs1634800	-0.044	135.861	-0.187	80.734	0.148	43.801
rs164594	0.086	68.315	-0.021	43.747	0.209	19.431
rs16857031	-0.104	40.765	0.007	25.708	-0.254	13.080
rs17457880	-0.320	10.654	-0.585	6.957	-0.014	2.834
rs17460657	0.064	30.522	0.007	20.232	0.354	6.734
rs17763769	-0.082	79.537	-0.006	49.806	-0.112	24.382
rs1805126	0.047	139.935	0.006	89.599	0.118	42.407
rs1983546	-0.145	142.907	-0.173	88.575	-0.018	44.355
rs2041678	-0.042	85.223	-0.107	50.951	0.035	27.601
rs2074238	-0.007	30.695	0.146	17.956	-0.265	8.884
rs2193565	-0.217	30.326	-0.451	19.665	0.106	7.686
rs2273042	-0.079	63.159	0.047	41.787	-0.283	15.850
rs2273905	-0.119	91.234	-0.215	54.311	0.092	29.657
rs236586	-0.017	146.038	-0.102	87.378	0.059	47.714

SNP=single nucleotide polymorphism; Non-isch=non-ischemic; SCD=sudden cardiac death; SE=standard error

| SNP	All Non-isch SCD Effect	All Non-isch Weights (1/SE²)	Non-isch Male SCD Effect	Non-isch Male Weights (1/SE²)	Non-isch Female SCD Effect	Non-isch Female Weights (1/SE²)
rs246185	-0.039	114.934	-0.125	68.457	0.051	37.983
rs2579344	0.203	69.531	0.344	41.115	-0.053	21.297
rs3026445	-0.075	140.452	-0.028	90.180	-0.143	41.438
rs347272	0.047	72.480	-0.034	44.862	0.278	24.936
rs3857067	0.119	131.764	0.177	80.122	-0.054	40.624
rs3902035	-0.034	123.778	-0.113	78.376	0.079	36.482
rs3922843	-0.129	84.806	-0.011	51.444	-0.378	24.880
rs4246215	-0.205	137.912	-0.178	85.724	-0.188	42.482
rs457162	-0.213	29.015	-0.396	14.703	-0.117	11.910
rs4656345	-0.210	19.877	-0.436	12.532	0.396	7.424
rs4784934	0.196	99.092	0.190	63.352	0.153	29.302
rs545833	-0.039	125.199	-0.069	82.294	0.040	36.570
rs6599250	-0.063	141.428	-0.136	84.842	0.069	46.406
rs6669543	0.167	85.615	0.104	51.733	0.307	29.820
rs6947240	0.022	75.073	-0.034	47.868	0.007	21.779
rs7122937	-0.043	114.017	-0.109	69.225	0.049	36.949
rs7174839	-0.045	136.754	-0.043	85.678	-0.094	41.706
rs7545047	0.147	21.097	0.180	11.713	-0.013	6.955
rs7561149	-0.039	141.382	0.036	87.182	-0.085	44.241
rs7681503	-0.175	131.881	-0.125	84.571	-0.305	40.763
rs8049607	0.004	122.513	0.019	73.220	0.008	39.507
rs8063949	0.137	80.338	0.154	49.674	0.114	25.308
rs808963	0.079	67.516	0.097	42.056	0.020	20.989
rs846111	0.073	92.609	-0.056	56.677	0.246	30.054
rs938291	-0.258	139.671	-0.221	88.410	-0.300	42.535
rs946267	-0.115	51.498	0.053	31.285	-0.662	11.900
rs9851710	0.115	119.964	0.043	73.085	0.249	36.933
rs9856587	0.123	67.073	0.176	43.011	0.037	19.305
rs9920	0.002	42.834	0.134	25.178	-0.068	14.628

SNP=single nucleotide polymorphism; Non-isch=non-ischemic; SCD=sudden cardiac death; SE=standard error

Figure S1. Multi-dimensional scaling (MDS) plot of Fingesture and NFBC1966 cohort samples.
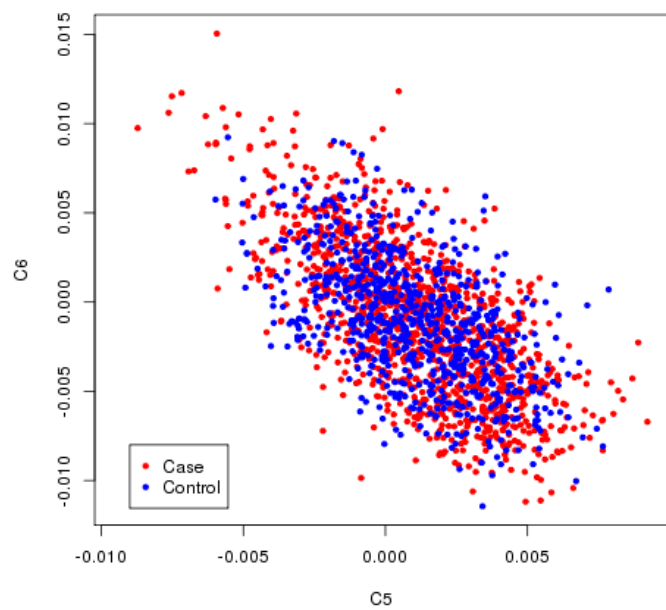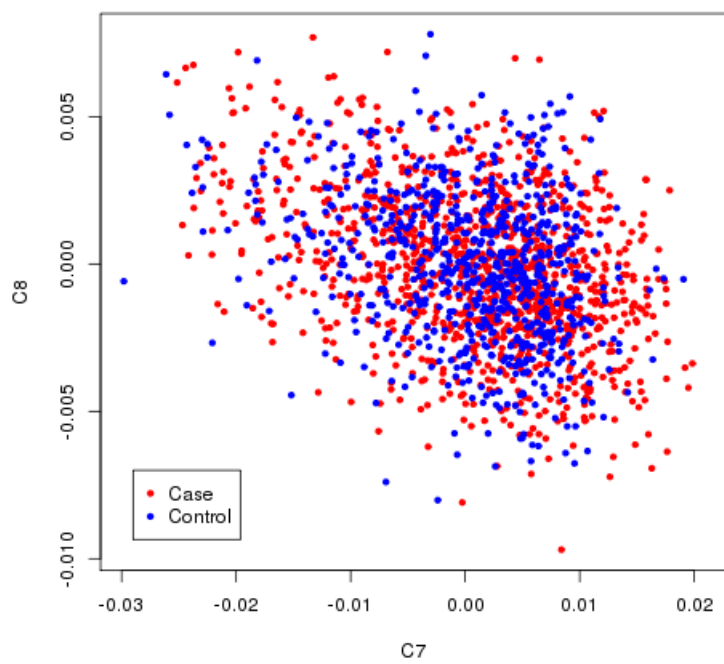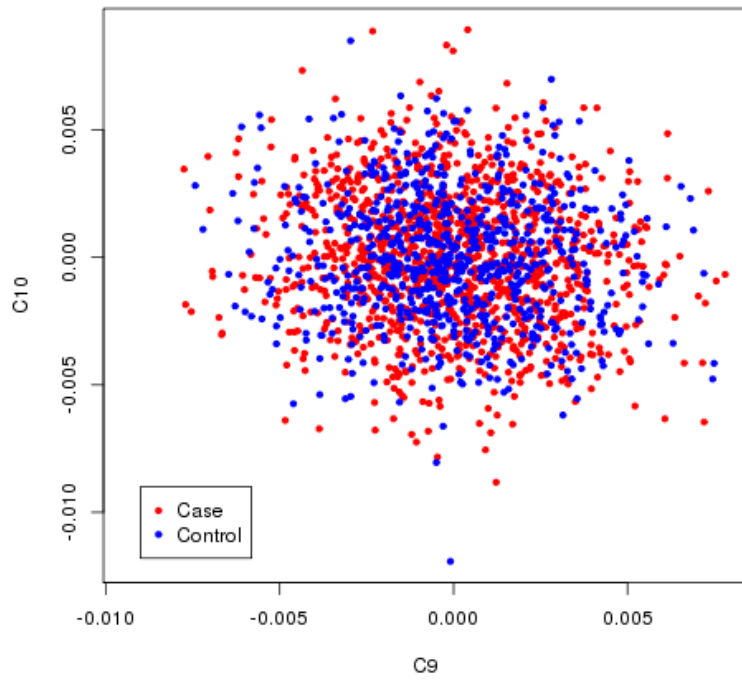
A.
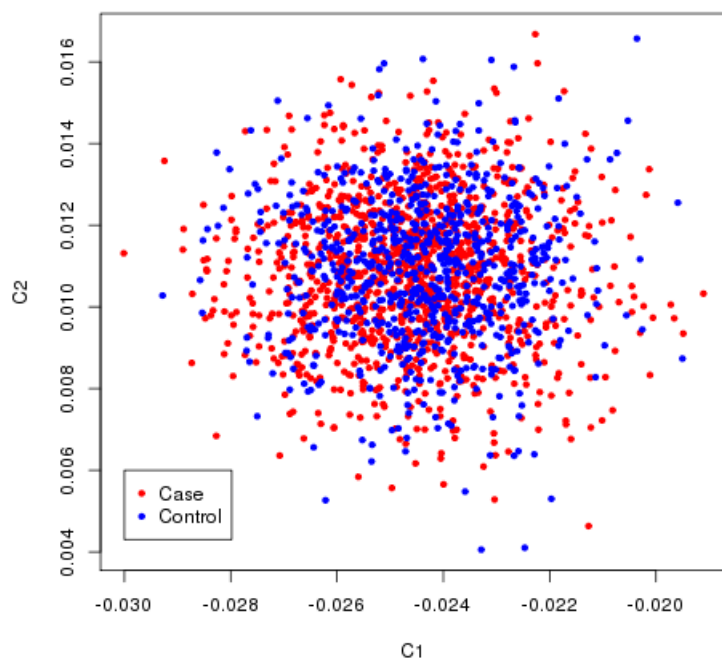
B.
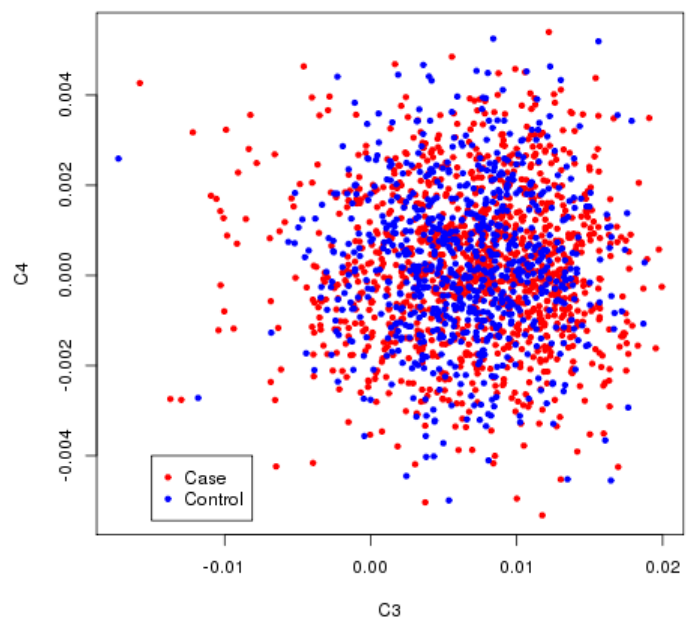
C.

D.

E.

 The plots A-E demonstrates strong genetic overlap between the Fingesture cohort (red) and the NFBC1966 cohort (blue).