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

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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
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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.

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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=1×10⁻²¹₃) and accounts for ≈1% of the variation in QT interval.20 This SNP has been previously associated with increased SCD risk21,22 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 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. The “other” individuals with SCD included individuals with the following conditions: myocarditis, cardiac anomaly, and individuals with a normal autopsy (e.g., 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 (i.e., 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. 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 (i.e., QT interval) and an outcome (i.e., 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. Mendelian randomization has other assumptions that must be met as well, including the absence of pleiotropy. 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. 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 (\( \beta_{\text{trait}} \)) to the association of the SNPs with SCD (\( \beta_{\text{outcome}} \)) using the R package “MendelianRandomization.” 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. Finally, we used the MR-Egger Intercept test to test for the presence of pleiotropy. \( P \) 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 were used in this analysis (1168 individuals with SCD and 761 Finnish 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 multistest 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, 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.

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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;
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Mendelian Randomization of QT Interval

Using Mendelian randomization approaches, we have previously established that QT interval is causally associated with SCD. 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. 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 \((1/SE^2)\), 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; \(P=0.018\)). 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, 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, 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
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. 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

![Figure 2](image-url)
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 substructure 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 randomization. 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 association 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 association 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.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL
| 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 criteria | Sample and SNP call rate (<95%); sex check; duplicate removal; cryptic relatedness; genetic outlier removal using PCA | Sample and SNP call rate (<95%); sex check; duplicate removal; cryptic relatedness; 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 relatedness; 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=principal component analysis; SCD=sudden cardiac death
| 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 | NOSIAP 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

| 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 |                                        |

| 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 |                                        |

| 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                                   |
| 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

| Dataset                              | cases/controls | SNPs included | GRSA Estimate [95% CI] | P     | P for ischemic/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  |                                       |
| Non-ischemic cases/population controls| 507/761       | 57            | 0.671 [-0.003, 1.340]  | 0.05  | 0.09                                  |

| Dataset                              | cases/controls | SNPs included | GRSA Estimate [95% CI] | P     | P for ischemic/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  |                                       |
| Non-ischemic cases/population controls| 387/354       | 57            | 0.386 [-0.445, 1.220]  | 0.36  | 0.43                                  |

| Dataset                              | cases/controls | SNPs included | GRSA Estimate [95% CI] | P     | P for ischemic/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  |                                       | 0.86                         |
| 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            |
| **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            |
| **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                   |
| rs1654594     | 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                | 35.340                   |
| 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             | -0.134              | 81.202                   | 0.217                 | 44.295                   |
| rs236856      | -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=standard error
| SNP         | All Isch SCD Effect | All Isch Weights (1/SE^2) | Isch Male Effect | Isch Male Weights (1/SE^2) | Isch Female SCD Effect | Isch Female Weights (1/SE^2) |
|-------------|---------------------|---------------------------|-----------------|---------------------------|------------------------|-----------------------------|
| 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                      |
| rs1256782   | 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=standard 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=standard error
| SNP          | All Isch SCD Effect | All Isch Weights (1/SE^2) | Isch Male Effect | Isch Male Weights (1/SE^2) | Isch Female SCD Effect | Isch Female Weights (1/SE^2) |
|--------------|---------------------|---------------------------|-----------------|---------------------------|------------------------|-----------------------------|
| 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                      |
| rs986587     | 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=standard error
| SNP            | All Non-isch SCD Effect | All Non-isch Weights (1/SE)² | Non-isch Male SCD Effect | Non-isch Male Weights (1/SE)² | Non-isch Female SCD Effect | Non-isch Female Weights (1/SE)² |
|----------------|-------------------------|------------------------------|--------------------------|-------------------------------|-----------------------------|-------------------------------|
| 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/SE^2) | Non-isch Male SCD Effect | Non-isch Male Weights (1/SE^2) | Non-isch Female SCD Effect | Non-isch Female Weights (1/SE^2) |
|------------|-------------------------|--------------------------------|--------------------------|-------------------------------|----------------------------|----------------------------------|
| 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.
The plots A-E demonstrates strong genetic overlap between the Fingesture cohort (red) and the NFBC1966 cohort (blue).