Discovery of genetic variation on chromosome 5q22 associated with mortality in heart failure

**S1 Text. Supplementary Materials, Methods and Results**

**1 Cohort descriptions**

The present study was initiated within the investigator-driven collaboration of the Cohorts for Heart and Aging in Genomic Epidemiology (CHARGE) consortium, including several population-based cohorts with genome-wide SNP data and comprehensive individual phenotyping [1,2].The discovery meta-analysis included participants from seven samples collected within five cohort studies. In a second stage, association was studied in individuals with new-onset heart failure from four independent cohorts. Participants were of European ancestry. The included cohorts are described in detail below. Definitions of incident HF employed in different studies are summarized in S1 Table.

**1.1 Stage 1 (discovery) cohorts**

**1.1.1 Atherosclerosis Risk in Communities study (ARIC and ARIC 2)** The ARIC Study is a prospective investigation of atherosclerosis and its clinical sequelae involving 15,792 individuals aged 45-64 years at recruitment (1986-1989). Subjects were selected by probability sampling from four communities: Forsyth County, NC; Jackson, MS (African-Americans only); Northwestern suburbs of Minneapolis, MN; and Washington County, MD. The initial clinical exams included a home interview to ascertain cardiovascular risk factors, socioeconomic factors, and family medical history, clinical examination and blood drawing for laboratory determinations. Medical events were identified by an annual phone interview, at a total of 4 three-year cycles of exams, and hospital and death certificate surveillance. A detailed description of the ARIC study design and methods has been published elsewhere [3].

For the purpose of this study, the cohort labeled ARIC represents the subset of individuals genotyped for genome-wide SNPs as previously described [2]. ARIC2 represents an independent subset of individuals that were genotyped for the same set of genome-wide markers and where not represented in the set of individuals described in Morrison et al, 2010. [1] Subjects of self-reported African American ancestry were excluded from the current study. For these analyses, measures of clinical and demographic characteristics were obtained from the clinical visit preceding HF onset. Deaths were defined as all-cause mortality. In the cohort labeled ARIC, deaths were ascertained through annual phone calls or through ongoing surveillance of health department death certificate files through December 31, 2004. In the cohort labeled ARIC2, deaths were ascertained through annual phone calls or through ongoing surveillance of health department death certificate files through December 31, 2005.

**1.1.2 Cardiovascular Health Study (CHS)** The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across four field centers [4]. The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled subsequently for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination in 1989-90. In 2007-2008, genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV [BeadChip](http://wildebeest.pbworks.com/BeadChip) system on 3980 CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping. A total of 1908 persons were excluded from the genome-wide association (GWA) study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. Because the other cohorts were predominantly of European ancestry, the African ancestry participants were excluded from this analysis to reduce the possibility of confounding by population structure.

Incident HF events were identified during follow-up by annual or semi-annual self-report and from administrative data [5]. Events identified by self-report or administrative data were validated by physician review of medical records using published criteria. Participant mortality was identified at 6-month surveillance contacts, National Death Index searches, and from obituaries. Additional information about cause of death was collected from death certificates, proxy interviews, and medical records [5].

**1.1.3 Framingham Heart Study (FHS)** The methods of recruitment and data collection have been described previously for the original Framingham Heart Study cohort (5,209 participants ascertained systematically from two-thirds of the households in the town of Framingham, MA, beginning in 1948) [6], the Framingham Heart Study Offspring cohort (5,124 children of the original cohort, and spouses of those children, beginning in 1972) [7], and the Third Generation cohort (4,095 children of the Offspring cohort, beginning in 2002) [8]. In the mid-1990s DNA was collected from the Original and Offspring study participants with the purpose of conducting genetic studies and developing cell lines. At the time of DNA draw, there were 4270 participants free of CHF in these two cohorts. Of these 4270, 249 individuals developed incident CHF. The current study was conducted in these 249 participants of the Original and Offspring cohorts, who were free of CHF at the time of their blood draw for a DNA sample and then developed incident CHF. Of the 249 with incident CHF, 156 died subsequently over the subsequent 10 years of follow up. There is continuous follow up for all cardiovascular and death events. An endpoint Committee consisting of three physicians reviewed all suspected congestive heart failure events to confirm occurrence of the event, using previously agreed criteria. The same committee also reviews all deaths. CHF is defined as satisfying the previously published Framingham criteria\* (presence of 2 major, or of one major plus two minor criteria in the absence of a competing explanation) and adjudicated by a panel of three experienced investigators. The major criteria are Paroxysmal nocturnal dyspnea or orthopnea, Distended neck veins, Hepatojugular reflux, Rales, S3 gallop, Enlarged heart by X-ray, Acute pulmonary edema on chest X-ray, Treatment induced weight loss >10lbs/5 days, Increased venous pressure > 16 cm water, Pulmonary edema and visceral congestion or cardiomegaly on autopsy. The minor criteria are Dyspnea on ordinary exertion, Night cough, Heart rate > 120/minute, Hepatomegaly, Ankle edema, Decrease in vital capacity by 1/3rd, Pleural effusion by X-ray and Pulmonary vascular engorgement by X-ray.

**1.1.4 Health, Aging and Body Composition (Health ABC)** The Health ABC Study is a population-based study of 3075 community-dwelling men and women aged 70 to 79 years at enrolment. To be eligible, participants had to report no difficulty in walking one-quarter mile or climbing 10 stairs without resting. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated zip code areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee, USA. Exclusion criteria included difficulties with activities of daily living, obvious cognitive impairment, inability to communicate with the interviewer, intention of moving within 3 years, or participation in a trial involving a lifestyle intervention. In addition, subjects with self-report African American ancestry were excluded from the current study. All participants provided written informed consent, and the institutional review boards at both study sites approved the study protocol. Baseline data were collected from April 1997 to June 1998. Buffy coat samples for subsequent DNA analyses were drawn at baseline visit.

Cardiovascular disease status at baseline, including prevalent heart failure, was based on self-reported history, use of selected drugs, and *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as reported by Medicare and Medicaid Services from 1995 through 1998. All participants were asked to report any hospitalizations, and every 6 months they were asked direct questions to elicit information about interim cardiovascular events. All admissions with an overnight stay were evaluated for cardiovascular events by reviewing the medical records at each site. All first admissions with an overnight stay confirmed to be related to heart failure were classified as incident heart failure. Local adjudicators classified events as heart failure based on symptoms, signs, chest radiograph results, and echocardiographic findings based on criteria similar to those used in the Cardiovascular Health Study [9]. The heart failure criteria required at least a heart failure diagnosis from a physician and treatment for heart failure (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator); these criteria have been used in previous investigations. Because heart failure was not allowed as a cause of death, there were no immediate deaths from incident heart failure. The Health ABC Study Diagnosis and Disease Ascertainment Committee reviewed all hospitalizations and deaths, and underlying causes of death were determined by central adjudication.

**1.1.5 Rotterdam Study (RS and RS2)** The Rotterdam Study is a prospective population-based cohort study to investigate the determinants of chronic diseases among participants aged 55 years and older, of which the methods have been described previously [10]. Briefly, all residents of Ommoord, a district of Rotterdam, the Netherlands, aged 55 years or older, were asked to participate in 1990. 7983 (78%) participated. The baseline examination, conducted in 1990-1993, consisted of a home interview and research center visit, during which blood samples were taken. After baseline examination, participants were invited to visit the research center for extensive testing every 3-4 years. In 2000, inhabitants who had turned 55 years or newly moved to the study district since the start of the study were invited to participate in the Rotterdam Study 2 (RS2). 3011 (67%) participated, who underwent the baseline examination (including blood sampling) and entered into the same follow-up program. During the baseline examination and follow-up visits, measurements are performed using standardized methods, including measurement of height, weight, systolic and diastolic blood pressure. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Dutch Ministry of Health, Welfare and Sport, implementing the “Wet Bevolkings Onderzoek: ERGO (Population Screening Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Follow-up for heart failure was complete until October 2006. The presence of heart failure was assessed using a validated score based on the definition of heart failure of the European Society of Cardiology [11]. Information on prevalent heart failure at baseline was available for all participants and participants with prevalent heart failure were excluded. Cases of incident heart failure were obtained by continuously monitoring participants of the Rotterdam Study during follow-up. The date of incident heart failure was defined as the day of the first occurrence of symptoms suggestive of heart failure, or the day of receipt of a first prescription for a loop diuretic or an inhibitor of angiotensin-converting enzyme in a patient diagnosed with heart failure, whichever came first. The diagnosis of heart failure was classified as definite, probable, possible, or unlikely. In accordance with the criteria of the European Society of Cardiology, only definite and probable cases were included in the analysis.

Deaths were ascertained through general practitioner medical records and from municipal records through January 1, 2007. The mortality ascertainment rate was greater than 99%.

**1.2 Stage 2 cohorts**

**1.2.1 The Malmö cohorts (Malmö Diet and Cancer and the Malmö Preventive Project)** Participants with prevalent or incident heart failure were identified from these two prospective, population-based cohort studies from the city of Malmö in southern Sweden. Baseline characteristics and endpoint ascertainment have been described in detail previously for both cohorts[12,13]. Informed consent was obtained from all participants and both studies were approved by the ethics committee of Lund University, Sweden.

The Malmö Diet and Cancer study (MDCS) included 30,447 randomly selected men born between 1923 and 1945 and women born between 1923 and 1950. Participants underwent a baseline examination between 1991 and 1996, with sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures, and filled out a questionnaire.

The Malmö Preventive Project (MPP) included 33,346 randomly selected men and women born between 1921 and 1949. Male participants (n = 22,444) underwent baseline examinations between 1974 and 1992 female participants (n = 10,902) underwent baseline examinations between 1980 and 1992. The present study was performed in the 17 284 participants who attended a reexamination between 2002 and 2006. At the reexamination, participants underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures, and filled out a questionnaire.

Prevalent and incident diagnoses of HF were identified by record linkage to national registers using personal identification numbers [14]; the Swedish Hospital Discharge Register (HDR) and the Swedish Cause of Death Register (CDR) [15]. Time of death was ascertained from the CDR. Both registers are administered by the Swedish National Board of Health and Welfare. Data collection in the HDR was started in the 1960s and includes dates of admission and discharge as well as primary and contributory diagnoses from all public hospitals in Sweden. Reporting to the HDR has been compulsory since 1987 but the only hospital in Malmö (Malmö University Hospital) has reported since 1969. The CDR includes diagnoses from death certificates since 1952, regardless if death occurred outside of Sweden. Diagnoses in the HDR are coded as primary or contributory and in the CDR as underlying or contributory cause of death, both using the International Classification of Disease (ICD). The 8th edition (ICD-8) was used until the end of 1986, the 9th edition (ICD-9) between 1987 and 1996 and the 10th edition (ICD-10) from 1997 until present. Heart failure was defined as diagnosis codes 427.00, 427.10, 428.99 (ICD-8), 428 (ICD-9), I50 or I11.0 (ICD-10) as primary or contributory diagnosis. High validity of such diagnoses have previously been reported [16].

**1.2.2 Physicians’ Health Study (PHS)** The Physicians’ Health Study is a completed randomized, double-blind, placebo-controlled trial designed to study low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer. DNA was extracted from blood samples collected between 1997-2001. All incident cases of HF occurring after blood collection among participants of European ancestry were included in the current study. A previous validation study of incident heart failure self-report confirmed valid diagnoses in 91% of cases [17]. Mortality was ascertained by an End Point Committee. Deaths were identified through systematic searches of the National Death Index for the entire enrollment cohort, and death certificates were obtained from state agencies for all deaths that occurred before February 1, 1988. The deaths were classified by trained nosologists according to the International Classification of Diseases, Ninth Revision (ICD-9), as previously described [18].

**1.2.3 Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)**A detailed description of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) has been published elsewhere [19,20]. PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements. At baseline, blood samples were drawn and DNA was extracted. A whole genome wide screening has been performed in the sequential PHArmacogenomics of Statins in the Elderly at risk study. Heart failure was one of the tertiary endpoints of the PROSPER study, all endpoints were adjudicated by an expert committee blinded to randomized study medication and using predefined criteria. Heart failure was defined based on a combination of symptoms (e.g. shortness of breath) and signs, including chest radiograph with fluid congestion or echocardiogram with severely diminished left ventricular function.

**2 Methods for genotyping and imputation across cohorts**

Genotyping, quality control, data cleaning and imputation was performed independently in each cohort using different genetic platforms and software as outlined below.

**2.1 Stage 1 (discovery) cohorts**

**2.1.1 Atherosclerosis Risk in Communities study (ARIC and ARIC2)** Genotyping used DNA collected from phlebotomy. Genome-wide assays of SNPs were conducted using the Affymetrix 6.0 platform. Quality control and data cleaning and imputation by MACH 1.0 with genome build NCBI35 was conducted in two phases. For the purpose of this study, the cohort labeled ARIC represents the subset of individuals described by Morrison et al[1] who were evaluated in the first phase of genotype quality control, data cleaning and imputation. ARIC2 represents an independent set of individuals that were evaluated in the second phase of genotype quality control, data cleaning and imputation. The methods for genotyping and imputation were identical for ARIC and ARIC2. The influence of population stratification was assessed using principal component analysis.

**2.1.2 Cardiovascular Health Study (CHS)** Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV [BeadChip](http://wildebeest.pbworks.com/BeadChip) system. Genotypes were called using the Illumina [BeadStudio](http://wildebeest.pbworks.com/BeadStudio) software. The following exclusions were applied to identify a final set of 306,655 autosomal SNPs: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap. Imputation was performed using BIMBAM v0.99 with reference to [HapMap](http://wildebeest.pbworks.com/HapMap) CEU using release 22, build 36 using one round of imputations and the default expectation-maximization warm-ups and runs. The influence of population stratification was assessed using principal component analysis.

**2.1.3 Framingham Heart Study (FHS)** Genotyping was conducted for the SNP Health Association Resource (SHARe) project (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\_id=phs000007.v10.p5) using the Affymetrix 500K mapping array (250K Nsp and 250K Sty arrays) and the Affymetrix 50K supplemental gene focused array on a total of 9,274 individuals from all three cohorts. Genotyping resulted in 503,551 SNPs with successful call rate >95% and HWE P>1.0x10-6 in 8,481 individuals with call rate >97%. Imputation of 2,543,887 autosomal SNPs in HapMap release 22, build 36, CEU sample was conducted using the algorithm implemented in MACH (version 1.0.15). From a total of 534,982 genotyped autosomal SNPs in Framingham, 378,163 SNPs were used in imputation after filtering out 15,586 SNPs (HWE P < 1.0x10-6), 64,511 SNPs (missingness > 0.03), 45,361 SNPs (mishap *P* < 1.0x10-9), 4,857 SNPs (> 100 Mendelian errors), 67,269 SNPs (frequency < 0.01), 2 SNPs (due to strand issues upon merging data with HapMap), and a further 13,394 SNPs that were not present on HapMap. We used 200 biologically unrelated participants to estimate the parameters of the imputation model and subsequently applied the estimated parameters to obtain imputed SNPs for all 8,481 participants. To evaluate population substratification, we conducted principal component analyses using EIGENSTRAT [21] on the genotypes from 882 unrelated participants. We estimated the first 10 principal components and applied the loadings of these components to all genotyped participants. Finally, we evaluated whether any of these principal components were associated with CHF. All analyses of individual SNPs adjusted for sex, age, generation (Original or Offspring Cohort), and principal components 1 and 3 using Cox proportional hazards models with robust standard errors calculated by clustering on families to account for familial correlations. The Framingham Heart Study was approved by the institutional review boards of Boston University and the National Institutes of Health. All participants provided written informed consent.

**2.1.4 Health, Aging and Body Composition (Health ABC)** Genotyping was performed using the Illumina 1M chip array. Genotypes were called using the Illumina BeadStudio software. The following exclusions were applied to identify a final set of 1,007,948 SNPs: call rate < 97%, MAF < 1% and HWE P < 10-6. Imputation was performed using MACH v1.16 with reference to HapMap CEU using release 22. In genetic association analyses, adjustment was performed for principal components.

**2.1.5 Rotterdam Study (RS and RS2)** Genotyping was done using the version 3 Illumina Infinium II HumanHap550 SNP chip array. Genotyping procedures were followed according to manufacturer’s protocol (Illumina, San Diego, CA, USA). Any samples with a call rate below 97.5%, excess autosomal heterozygosity, mismatch between called and phenotypic gender, or outliers identified by the IBS clustering analysis with > 3 standard deviations from population mean or IBS probabilities >97% were excluded from the analysis; in total, 5,974 samples were analyzed in RS and 2,157 in RS2. SNPs with minor allele frequency ≤ 1%, SNP call rate < 98% for Hardy-Weinberg deviations with p< 1x10-6 were excluded. Comparison of genotype accuracy was performed against 22 Taqman SNPs and demonstrated less than 0.3% discrepancy across genotyping methods. In addition, intensity cluster plots of replicated SNPs at genome-wide significant level were visually inspected for erroneous genotype assignment.

The data was examined for potential population stratification after excluding outliers detected by the IBS clustering analysis. There was no evidence for significant population stratification affecting the results.

Imputation was conducted using the algorithm implemented in MACH. To get imputed data more restrictive SNP filters including a minor allele frequency > 0.01, SNP Call Rate > 0.98, and HWE *P*-value > 1x10-6 were applied. In total 2,543,887 SNPs were imputed using phased haplotypes of HapMap CEU trios.

**2.2 Stage 2 cohorts**

**2.2.1 The Malmö cohorts (Malmö Diet and Cancer and the Malmö Preventive Project)** DNA extracted from peripheral blood cells was assigned to batches without regard to heart failure status, survival or personal identity. Batches were genotyped with the same set of reagents using the Sequenom iPlex assay on a MALDI-TOF mass spectrometer (MassArray, Sequenom, San Diego, CA, USA). Sequenom reagents and protocols were used with 10 ng DNA as PCR template, according to the manufacturer’s instructions. Genotype calls were obtained using MassArray Typer 4.0 software (Sequenom, San Diego, CA, USA) and fluorescence intensity plots were manually inspected and curated.

**2.2.2 Physicians’ Health Study (PHS)** DNA extracted from peripheral blood cells was assigned to batches without regard to heart failure status, survival or personal identity. Batches were genotyped with the same set of reagents using the Sequenom iPlex assay on a MALDI-TOF mass spectrometer (MassArray, Sequenom, San Diego, CA, USA). Sequenom reagents and protocols were used with 10 ng DNA as PCR template, according to the manufacturer’s instructions. Genotype calls were obtained using MassArray Typer 4.0 software (Sequenom, San Diego, CA, USA) and fluorescence intensity plots were manually inspected and curated.

**2.2.3 Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)** The genome wide association study was conducted using the Illumina 660K-Quad beadchips following manufacturer’s instructions. After a stringent quality control 557,192 SNPs in 5,244 subjects were available for analysis. To maximize the availability of genetic data and coverage of the genome, imputation up to 2.5 million autosomal CEPH HapMap SNPs was performed with MACH imputation software based on the Hapmap built II release 23.

**3 In silico studies of effect on cardiac structure and function**

The association of the replicated SNPs with measures of cardiac structure and function was evaluated by lookup in summary results from the following GWA studies: EchoGen, CHARGE-HF, CHARGE-QRS, QT-IGC, and the sudden cardiac death genetics consortium.

**3.1 EchoGen**

The EchoGen study examined the association of 2.5 M genome-wide SNPs with echocardiographic phenotypes in 12,612 individuals of European ancestry from 5 community-based cohorts (Cardiovascular Health Study, Framingham Heart Study, Rotterdam Study, Gutenberg Health Study, Monica-Kora) and has been published previously [22]. Phenotypes under study include left ventricular fractional shortening, dichotomous systolic function (defined as fractional shortening < 0.29 or ejection fraction < 0.50) and cardiac dimensions (left ventricular mass, left ventricular wall thickness defined as the sum of the posterior wall thickness and the interventricular septum, left ventricular internal diastolic dimension, left atrial size, and aortic root size). The association of each SNP with each trait was analyzed in additive models adjusted for age, sex, height and weight. Effect estimates from individual studies were combined using inverse variance-weighted meta-analyses.

**3.2 CHARGE-HF**

The CHARGE-HF study examined the association of 2.5 M genome-wide SNPs with incident heart failure in 20,926 individuals from four community-based cohorts also included in the present study: ARIC, CHS, FHS and the Rotterdam Study. SNPs were in each cohort related to incident HF (n = 2,526) during a mean follow-up of 11.5 years, using Cox proportional hazards models adjusted for age and sex. Results were combined using inverse variance-weighted meta-analysis. These results from CHARGE-HF have been published previously [23].

**3.3 CHARGE-QRS**

The CHARGE-QRS study tested the association of electrocardiographic QRS duration with genome-wide SNPs in 14 cohorts, comprising 40,407 European-ancestry subjects in total. A total of ~2.5 million Hapmap II imputed SNPs were tested using a linear regression model with adjustment for age, gender, height and body mass index (and study site as appropriate). Genomic control was applied on a per-study basis. The regression results were meta-analyzed using inverse variance weighted fixed-effect models and again adjusted for the inflation factor. Details of the study populations and analytic methods have been published previously (24).

**3.4 Natriuretic Peptides in the Malmö Diet and Cancer Study**

Genotyping of genome-wide SNP data was performed in the cardiovascular cohort of the Malmö Diet and Cancer Study described above, using the Illumina Human Omni Express Bead Chip. The cardiovascular cohort has been described previously [16] and includes ~5,500 random subjects from the general population included in the study between 1991 and 1994 with blood samples available. Atrial and B-type natriuretic peptides were measured using standard assays as previously described (16). A genome-wide association study of these two biomarkers was performed (manuscript in preparation), regressing each natriuretic peptide on genome-wide SNP data adjusting for age and sex using PLINK. Additive genetic models were used. Minimal inflation of test statistics was observed, and genomic control was applied.

**3.5 QT-IGC**

The QT-IGC study tested the association of electrocardiographic QT duration with genome-wide SNPs in 31 cohorts, including a total of 76,061 subjects of European ancestry. A total of ~2.5 million SNPs imputed to HapMap II were tested using a linear regression model with adjustment for age, gender, RR interval (inverse heart rate), and principal components of genetic ancestry using an additive genetic model. Individual study results were combined using meta-analysis with inverse variance weighted fixed-effect models [25].

**3.6 CHARGE-SCD consortium**

The CHARGE-SCD consortium carried out a genome-wide association study for sudden cardiac death with 4,496 cases and over 25,000 controls of European descent from 10 cohorts: Atherosclerosis Risk in Communities study (ARIC), FinGesture, Oregon Sudden Unexpected Death Study (Oregon-SUDS), Cardiac Arrest Blood Study (CABS), CARTaGENE study, Helsinki Sudden Death Study (HSDS), Rotterdam Study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS) and Harvard cohorts (SCD cases and matched controls from the Physicians Health Study (PHS I and II), the Nurses’ Health Study (NHS), the Health Professionals Follow-up Study (HPFS), and the Women’s Antioxidant Cardiovascular Study (WACS)). The data was analyzed using a Cox proportional hazards model for prospective studies and logistic regression for case-control studies adjusting for age, sex and additional study-appropriate covariates.  Subsequent meta-analysis was performed using standard inverse-variance fixed-effects models after adjusting for appropriate genomic control factor for each study. (manuscript in preparation)

**4 Results of in vitro assessment of enhancer activity**

To experimentally test the effect of rs9885413 on enhancer activity, the 100 bp region flanking the SNP (50 bp on either side) was cloned into a reporter vector. This region includes the entire predicted NHLH1-binding motif. One construct was designed to correspond to the major allele of rs9885413 (pGL3P-G) and one to the minor allele (pGL3P-T). NHLH1 is widely expressed in human tissues, and expression was confirmed in the human embryonic kidney cell line HEK293 cells from GeoProfiles (http://www.ncbi.nlm.nih.gov/geoprofiles/) and by qPCR. The reporter vectors were transfected into HEK293 and luciferase activity was measured after 24 hours. As seen in **S4 Fig**, the signal from the pGL3P-T construct was increased 4-fold compared with pGL3P-G (*P* < 0.001), indicating that the minor allele of rs9885413 substantially increases enhancer activity.

**5 Effects of rs9885413 on gene expression**

To test effects of rs9885413 on gene expression, we first studied gene expression *in silico* in the diverse tissues from the Gene-Tissue Expression (GTEx) project [28]. No gene was significantly associated with rs9885413 after correction for multiple tests (**S8 Table**). However, these analyses were limited by a relatively small sample size, with up to 168 samples (for blood) and only 87 samples for the left ventricle.

We next assessed association of the SNP with gene expression in two large datasets with each of the tissues most relevant for the phenotype under study: heart tissue and whole blood. First, gene expression in 247 left ventricular samples from patients with advanced heart failure (n=116) undergoing transplantation and from unused donors (n=131) were profiled using Affymetrix gene expression arrays. Two of the five genes at the locus (**Fig 1**) had lower expression than background noise in both subjects with and without heart failure (*TSLP* and *CAMK4*) as shown in **S9 Table**. Of the three expressed genes, only *TMEM232* was significantly associated with the SNP rs9885413 (*P* = 2.2x10-6). However, another SNP at the locus (rs244412) was more strongly associated with *TMEM232* expression (*P* = 3.6x10-19), and the association with rs9885413 was abolished in analyses conditioning for this SNP (*P* = 0.11). The SNP rs244412 was not significantly associated with HF mortality, indicating that the *TMEM232* eQTL signal likely reflects a separate signal at the locus. Cardiac expression of *TMEM232* was also very low (**S9 Table**). Next, we tested the association of rs9885413 with the expression of genes at the locus (+/- 500 kb) in whole blood from 5257 FHS participants [29], and with DNA methylation at cg02061660 among 2262 FHS participants. All five genes at the locus except *TMEM232* were expressed in blood. Expression of one gene (*TSLP*) was significantly associated with the methylation status of cg02061660 (*P* = 1.1x10-4). We did not observe association of the SNP rs9885413 with any transcript.

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