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Common β Adrenergic Receptor Polymorphisms Are Not Associated with Risk of Sudden Cardiac Death in Patients with Coronary Artery Disease

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Abstract

Background—Previous studies suggest β adrenergic receptor (βAR) single nucleotide polymorphisms (SNPs) are associated with out-of-hospital sudden cardiac death (SCD) and overall mortality, but did not specifically examine risk of ventricular arrhythmias (VA).

Objective—We examined the effects of functional SNPs of β1AR and β2AR on the risk of VA and SCD in patients with coronary artery disease (CAD).

Methods—β1AR (Ser49Gly, Arg389Gly) and β2AR (Gly16Arg, Gln27Glu) SNPs were genotyped in a case-control study comparing 107 patients with CAD and aborted SCD due to VA to 287 CAD controls and 101 healthy controls. These variants were also examined in the Heart and Estrogen Replacement Study (HERS) cohort of women with CAD followed for SCD (n = 66) and non-fatal VA (NFVA) (n = 33) over 6.8 years.

Results—In the case-control study, no statistically significant association was observed for odds of SCD with any of the SNPs or haplotypes tested. Similarly, HERS revealed null effects for these

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SNPs and haplotypes in relation to risk of SCD, SCD + NFVA, and all-cause mortality. Point estimates and confidence intervals for risk of SCD associated with β2AR27 were similar in both populations (Glu27 carriers vs. Gln27 homozygotes: adjusted OR 1.23 [95% CI 0.75–2.03, p=0.41] in the case-control study, and adjusted RR 1.18 [95% CI 0.69–2.00, p=0.55] in HERS). These null findings trend in the opposite direction and differ from previous published estimates (p=0.01 and 0.07, respectively).

Conclusion—We did not find an increase in risk of SCD associated with any of these common βAR polymorphisms.

Keywords

sudden cardiac death; ventricular arrhythmias; genetics; beta adrenergic receptors; coronary artery disease

Introduction

Sudden cardiac death (SCD) remains a major public health problem, accounting for nearly half a million deaths in the U.S. in 1999.[1] Nearly 80% of SCD occurs in the setting of coronary artery disease (CAD).[2] Ventricular tachycardia (VT) or ventricular fibrillation (VF) is the initiating event in the majority of SCD cases.[3] Ejection fraction (EF) remains the only major criterion to stratify patients for risk of SCD and implantable cardioverter-defibrillator (ICD) implantation, but this strategy alone is insensitive and nonspecific.[4] Genetic susceptibility to SCD in the setting of CAD is supported by several epidemiologic studies demonstrating that a family history of SCD is an independent risk factor for SCD and primary VF.[5, 6, 7]

Sympathetic activation, mediated by the β adrenergic receptors β1AR and β2AR, favors the development of ventricular arrhythmias (VA) and SCD.[2, 8–12] Two common nonsynonymous single nucleotide polymorphisms (SNPs) in each of the single-exon β1AR and β2AR genes are observed: β1AR Ser49Gly and Arg389Gly, and β2AR Gly16Arg and Gln27Glu, the latter two of which are in linkage disequilibrium (LD).[13] Carriers of the β1AR Gly49 allele are associated with a better survival in congestive heart failure (CHF)[14], while the β1AR Gly389 allele is associated with a lower risk for VT.[15] β2AR Gly16Arg and Gln27Glu result in altered receptor downregulation and trafficking in transfected cells.[16] Recent evidence also suggests a role of these β2AR SNPs in survival and pharmacogenetic response to β blockers following acute coronary syndrome (ACS)[17], and in the risk for out-of-hospital sudden death.[18] Both studies found a higher risk associated with the Gln27 homozygous genotype. However, neither study investigated the role of these polymorphisms specifically in the development of VA.

To specifically address these issues, we examined the potential role of these functional β1AR and β2AR variants in the risk of VA and SCD in the setting of CAD in two association studies with distinct study populations. Using a case-control design, we studied a group of patients with a history of myocardial infarction (MI) who had aborted SCD with documented VA, and compared them to two control groups, one with and one without CAD. In an independent study, we sought to validate our case-control findings in the large Heart and Estrogen Replacement Study (HERS) cohort of postmenopausal women with established CAD who were followed prospectively for SCD, VA, and other cardiac events.

Methods

The UCSF Committee on Human Research approved all protocols. Informed consent was obtained from all participants for DNA isolation and plasma collection.

Study Populations

UCSF SCD Case-Control Study—Consecutive cases of aborted SCD presenting to UCSF Medical Center Emergency Department or inpatient cases of aborted SCD at UCSF Medical Center between January 2000 and June 2006 were screened. Aborted SCD was defined as a cardiac arrest with documented sustained monomorphic VT or VF requiring cardioversion or defibrillation, exclusive of torsades de pointes (drug-induced QT prolongation or otherwise). Because we were interested in the most common phenotype of SCD, that occurring in the setting of CAD, only patients with a history of MI were included in this study. Thirty-one SCD cases occurred in the setting of acute ischemia, while 76 SCD cases occurred in the absence of active ischemia. Thus, SCD cases consisted of 107 patients with aborted SCD and a history of MI.

Two control populations were collected from the UCSF Genomic Resource in Arteriosclerosis, a population-based study of atherosclerotic heart disease.[19] In order to specifically address the risk for SCD and VA rather than CAD, a CAD control group was identified from patients presenting to the UCSF Cardiology Service and consisted of individuals with prior MI and documented CAD by coronary angiography (≥70% stenosis in ≥1 major arteries) or revascularization procedures. From a cohort of over 16,000 patients, potential CAD Controls were matched on a group level to the SCD Cases with respect to age at index MI ± 5 years, sex, ethnicity, degree of CAD as defined by revascularization procedure (coronary artery bypass graft surgery [CABG] > percutaneous transluminal angioplasty [PTCA]/stent), and duration of follow up since index MI. We then randomly selected 300 patients who were considered as CAD controls. Thirteen patients were excluded when they were found to have had SCD, leaving 287 patients who were used as CAD Controls.

As a “supercontrol” group, a non-CAD Control group consisting of healthy individuals without known coronary or other disease in their ninth decade of life was selected from the control arm of the UCSF Genomic Resource in Arteriosclerosis. From a cohort of over 3800 participants, potential non-CAD Controls were matched to cases on a group level with respect to sex and ethnicity. We then randomly selected 107 patients who were considered as non-CAD controls. Six patients were excluded when they were found to have had cardiac deaths, leaving 101 patients who served as non-CAD Controls.

Participants in both control groups were confirmed to have been free of VA, SCD, or implantation of an ICD by searching the UCSF electronic medical record and UCSF ICD database, direct phone interview with participant and/or next of kin, and a search of the National Death Index up to August 2006. Any participant found to have had VA or SCD was excluded.

HERS Cohort SCD Study—HERS methods have been previously described.[20, 21] Briefly, participants were postmenopausal women with known stable CAD defined by previous MI, CABG, PCI, or angiographic evidence of ≥ 50% stenosis of ≥ 1 major coronary arteries. Participants in HERS were randomly assigned to 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate daily (n=1380) or placebo (n=1383). The HERS randomized controlled trial was conducted over 4.1 years, after which women were observed for an additional 2.7 years on average (HERS II).[22] Records of all hospitalizations were reviewed, and an independent morbidity and mortality subcommittee blinded to treatment assignment adjudicated all suspected outcome events, including SCD and non-fatal VA requiring resuscitation (NFVA). SCD outcome was defined as an unexpected, non-traumatic, non-self-inflicted fatality in participants who died within one hour of the onset of terminal symptoms; NFVA was adjudicated as VF and unstable VT that required electrical cardioversion. DNA was collected in 2223 of the 2763 women in the combined HERS I/II cohort following retrospective consent for genetic material.

SNP Selection and Genotyping

Patients were genotyped for β1AR Ser49Gly (rs1801252) and Arg389Gly (rs1801253) and β2AR SNPs Gly16Arg (rs1042713) and Gln27Glu (rs1042714).

DNA was extracted from peripheral blood lymphocytes (Gentra Systems) for the UCSF SCD Case-Control Study. DNA from HERS participants was isolated from stored Pap smear slides using polymerase chain reaction (PCR) amplification. Genotyping was performed blinded to clinical status; positive and negative controls were included. Three polymorphisms were genotyped by the template-directed dye-terminator incorporation assay with fluorescence polarization detection[23, 24] using the AcycloPrimeFP II kit (Perkin-Elmer) and read on the EnVision microplate reader (Perkin-Elmer). PCR conditions and primer sequences are shown in Supplemental Table 1. β1AR Arg389Gly was genotyped using the TaqMan Assay (Applied Biosystems, Assay ID: C_8898494_10) and read on the ABI PRISM 7900HT Sequence Detection System (PerkinElmer). When indeterminate readings or discrepancies appeared, plates were repeated or genotyping results were verified by sequencing. Genotyping of HERS participants was performed using the MassArray SNP Genotyping System (Sequenom, Inc.) (primers available upon request). Ninety-nine percent (2199 of 2223) of the HERS participants with available DNA were genotyped. Of these, unambiguous genotypes were determined for 2172 (β1AR49), 2139 (β1AR389), 2134 (β2AR16), and 2129 (β2AR27) participants.

Statistical Analysis

UCSF SCD Case-Control Study—Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed using the appropriate chi-square test. We used multivariate logistic regression to assess the effects of each SNP on odds of SCD, controlled for all factors on which cases were frequency-matched to controls: sex, race/ethnicity, years since index MI, and degree of CAD.[25] We evaluated four genetic models for each SNP: dominant, recessive, log additive, and codominant. We repeated the analyses restricted to Caucasians and compared the odds of SCD according to β2AR haplotypes imputed using Bayesian methods,[26] as implemented in the PHASE version 2.1 software package [http://www.stat.washington.edu/stephens/software.html].

HERS Cohort SCD Study—We used unadjusted Cox regression for time to SCD, NFVA, or their composite, including the 4 genetic models. We repeated the analyses adjusting for race/ethnicity, age, current smoking, number of MI, use of β blockers at baseline, CHF, diabetes, and hypertension, as well as stratifying by race/ethnicity and β blocker use. We also examined β2AR haplotype effects.

Comparison with External Estimates—We used Z-tests to compare our log odds and hazard ratio estimates with those from the literature. Variances of the external estimates were computed from confidence intervals.

Results

UCSF SCD Case-Control Study

The vast majority of CAD controls (90.9%) and non-CAD controls (100%) were confirmed to have been free of VA or SCD by direct telephone contact and/or a search of causes of death by National Death Index in August 2006. Characteristics of the patients in the SCD cases and the two control groups are shown in Table 1. SCD cases had a higher prevalence of current smoking as compared to CAD controls. While EF determination was available in a majority of SCD cases (89 of 107) within 1–2 days of SCD, only a minority of CAD controls (89 of 287) had EF available near the time of index MI (1–3 months). Among these cases and CAD controls, mean EF was significantly lower for cases (33 ± 12 vs. 52 ± 14, $p < 0.01$). Age at

index MI was comparable for SCD cases (57.1 ± 14.2) and CAD controls (57.1 ± 12.4); mean age of the non-CAD control group was 83.7 ± 5.5 years. With the exception of ACE-I/ARB, medication use was comparable between SCD cases and CAD controls.

SNP Analysis—Genotype frequencies for each SNP are shown in Table 2. No SNP deviated from Hardy-Weinberg expectations. β2AR Gly16Arg and Gln27Glu were in LD, thus 3 common haplotypes were constructed, H1 (Gly16-Glu27), H2 (Arg16-Gln27), and H3 (Gly16-Gln27). The observed allele and haplotype frequencies differed by ethnicity and were comparable to those for the general US population.[13]

We observed no association between the 4 SNPs and odds of SCD for cases compared to both control groups for all 4 genetic models. Odds ratios for SCD for Case vs. CAD Control and Case vs. Non-CAD Control comparisons for the dominant and recessive models are presented in Figure 1. Analyses adjusted for ethnicity, sex, number of years of follow-up since index MI, and severity of CAD are shown. Analyses restricted to Caucasian individuals or males, also indicated no association between odds of SCD and the 4 SNPs tested (Supplemental Tables 2 and 3). Among Caucasian individuals, comparison of SCD cases to CAD and non-CAD control groups yielded adjusted ORs for SCD for β2AR Glu27 carriers as compared to Gln27 homozygous individuals of 1.47; (95% CI 0.83–2.61, p=0.18) and 0.97 (95% CI 0.49–1.92, p=0.92), respectively.

Haplotype Analysis—β2AR haplotype analysis for odds of SCD as compared to the CAD control group indicated no association. H2 (Arg16-Gln27) and H3 (Gly16-Gln27) carriers had similar ORs for SCD as compared to reference H1 (Gly16-Glu27) carriers (ORs 1.06, 95% CI 0.61 to 1.82, p=0.844 for H2 and 1.07, 95% CI 0.63 to 1.79, p=0.808 for H3, adjusted for ethnicity, sex, number of years of follow-up since index MI, and severity of CAD). The OR for SCD among those who lack the H1 haplotype was also comparable to reference H1 carriers (0.81, 95% CI 0.49–1.35, p=0.427). Furthermore, diplotype analysis demonstrated no difference for odds of SCD, as compared to individuals with the common diplotype (i.e., H1H2).

HERS Cohort SCD Study

In the combined HERS I/II cohort, 136 of 2763 (4.9%) women suffered SCD over a mean follow-up of 6.8 years and 50 (1.8%) women suffered NFVA. Retrospective consent from relatives could not be obtained for some deceased HERS participants, therefore DNA was available in 66 of 136 SCD cases and 33 of 50 NFVA cases. Of the 2223 participants with DNA, 2125 participants were free of SCD or VA and served as the reference group. No differences were observed in the baseline characteristics between the subset of HERS participants who suffered SCD, SCD+NFVA, and all-cause mortality, compared with the subset of participants that were genotyped (Supplemental Table 4). There was no difference in SCD events between the hormone replacement (E+P) and placebo arms (67 vs. 69, respectively), while there was a statistically significant doubling of NFVA in the E+P arm (33 vs. 17, p=0.02).[22]

SNP analysis—There were no differences in baseline characteristics by β1AR49, β1AR389, β2AR16, or β2AR27 genotype (Tables 3A and 3B). Allele frequencies for each SNP are shown in Table 4. None of the SNPs deviated from Hardy Weinberg equilibrium. β2AR Gly16Arg and Gln27Glu were in LD, and the 3 common haplotypes described above were constructed. The observed allele and haplotype frequencies differed by ethnicity, and were similar to those obtained in the SCD Case Control study and previous reports.[13, 18]

Risk for the outcomes of SCD, SCD + NFVA, and all-cause mortality, were examined for each SNP under the 4 genetic models. The risks for SCD, SCD + NFVA, and all-cause mortality as assessed by the dominant and recessive models for all SNPs tested are shown in Figure 2. Analyses adjusted for ethnicity, age, number of MI, baseline β blocker use, smoking status, CHF, diabetes, and hypertension are presented. Kaplan-Meier analysis of the cumulative incidence of SCD, SCD + NFVA, and all-cause mortality in the HERS cohort by β2AR genotype revealed no suggestion of time-dependent interaction (Supplemental Figures 1 and 2).

Though no association was observed for risk of SCD or SCD + NFVA, we did observe a trend towards increased risk for all-cause mortality for β2AR Glu27 carriers as compared to Gln27 homozygous individuals (adjusted RR 1.27; 95% CI 0.97–1.67, p=0.086). Analyses restricted to Caucasian participants or stratified by β blocker use at baseline also demonstrated no association for risk of SCD, SCD+ NFVA, or all-cause mortality for any of the SNPs tested (data not shown). Among Caucasian HERS participants, the adjusted RR for all-cause mortality for β2AR Glu27 carriers as compared to Gln27 homozygous individuals was 1.22; 95% CI 0.91–1.63, p=0.175.

Haplotype Analysis—A haplotype analysis for β2AR Gly16Arg and Gln27Glu demonstrated no association for risk of SCD or SCD + NFVA in the HERS cohort. H2 and H3 carriers had similar HRs for SCD and SCD + NFVA as compared to reference H1 carriers (HRs for SCD 0.84, 95% CI 0.50 to 1.41, p=0.50 for H2 and 0.89, 95% CI 0.52 to 1.53, p=0.67 for H3, adjusted for ethnicity, number of MI, baseline β blocker use, smoking status, history of CHF, diabetes mellitus, and hypertension). The HR for SCD among those who lack the H1 haplotype was also comparable to H1 carriers (0.87, 95% CI 0.51–1.49, p=0.61). Analysis by diplotype demonstrated no difference for hazard of SCD or SCD + NFVA by diplotype, as compared to individuals with the common H1H2 diplotype.

Discussion

In the present study, we demonstrate a lack of association between the common functional β1AR and β2AR genetic variants and SCD due to VA in the setting of CAD. Rigorously phenotyped case and control population samples were collected, with documented presence or absence of CAD and VA. The UCSF SCD Case-Control Study findings were replicated in a large cohort of post-menopausal women with documented CAD that was closely followed for adjudicated SCD and VA events.

These nonsynonymous β1AR and β2AR SNPs were chosen as candidates based on their resultant functional changes in receptor activity and the role of the sympathetic system in potentiating the development of VA. *In vitro* and *in vivo* studies have shown higher sympathetic activity of the β1AR Arg389 and Ser49 alleles.[27] Experiments in human and transfected cell systems demonstrated blunted agonist-mediated receptor downregulation of the β2AR Arg16 and Glu27 variants.[28] Sympathetic stimulation and βAR signaling play an important role in both mechanisms for arrhythmogenesis in the setting of CAD captured in our study: primary VF related to acute plaque rupture and ischemia, and scar-mediated VA. Our null results suggest that, while there may be functional differences resulting from these amino acid substitutions, these changes do not result in substantial differences in arrhythmic SCD risk in the setting of CAD.

The β2AR Gln27 homozygous genotype has been linked to both a higher risk for SCD and higher overall mortality among ACS patients discharged on β blocker therapy.[17, 18] Sotoodehnia, et. al. reported a higher risk of SCD for Gln27 homozygotes as compared to Glu27 carriers in both an elderly cohort at risk for CAD (adjusted HR 1.50, 95% CI 1.12–2.00

in the Cardiovascular Health Study [CHS]) and a replication study in Caucasians comparing 155 SCD cases to 144 community-based controls (adjusted OR 1.83, 95% CI 1.11–3.04 in the Cardiac Arrest Blood Study [CABS]).[18]

Our findings for risk of SCD among Gln27 homozygotes vs. Glu27 carriers are inconsistent with the earlier findings. We detected a statistically significant difference in a comparison of the results of the case-control studies, (p=0.01 by Z-test for comparison of results for CABS and the UCSF SCD Case-Control Study, restricted to Caucasians) and a suggestive difference for the comparison of the results of the cohort studies (p=0.07 for comparison of results from CHS and HERS). Moreover, the point estimates in both of the current studies suggest a slightly decreased, rather than significantly increased, risk for SCD for Gln27 homozygotes as compared to Glu27 carriers: for SCD cases vs. CAD controls, adjusted OR 0.81 [95% CI 0.49–1.33], inverted from OR presented in Figure 1; for SCD in the HERS cohort, adjusted RR 0.85 [95% CI 0.50–1.45], inverted from RR presented in Figure 2 (risk estimates inverted since our analyses treated the Gln27 allele – the more common allele – as the reference). The upper bound of the confidence intervals of both of our studies indicate that it is highly unlikely that Gln27 homozygosity is associated with more than a 33–45% increase in SCD risk.

There are several potential explanations for this discrepancy. Because of our approach to selecting participants, a large majority of UCSF SCD cases (103 of 107) survived their cardiac arrest. Thus a "survival effect" of the Glu27 carriers may be operative in our SCD cases. However, very similar point estimates were observed for the "true" SCD outcome as well as the combined outcome of SCD + NFVA (a phenotype similar to the UCSF SCD cases) in our HERS cohort. There were also notable phenotypic differences in study populations due to differences in enrollment criteria. The HERS population was exclusively female and somewhat younger than the CHS population (mean age 66 years vs. 73 years). In the UCSF SCD study, only patients with documented VA as the cause of SCD were included. In the CHS and CABS studies, SCD cases included many out-of-hospital sudden deaths as determined by paramedic and chart records, without restriction to those with VA. Thus, the resulting SCD cases may have been more heterogeneous with asystolic, respiratory, and pulseless electrical activity arrests[3] as well as other "sudden" cardiac deaths such as some CHF deaths. Finally, both of the current study populations were selected from individuals with known CAD, rather than from a general population of individuals at risk for CAD. Therefore, some of the SCD cases in CHS and CABS may actually have been unrelated to CAD, and it is possible that the Gln27 homozygous genotype may be related to non-cardiac and/or nonarrhythmic sudden deaths that were counted as out-of-hospital SCD by paramedics.

Our HERS data also indicate a trend toward decreased (rather than increased) mortality for the Gln27 homozygous genotype as compared to Glu27 carriers among postmenopausal women with CAD, adjusted for β blocker use (p=0.086). Stratification among only β blocker users in HERS attenuated this trend (p=0.14). These results are inconsistent with Lanfear, et al's finding of an increased risk for overall mortality among homozygous Gln27 ACS patients treated with β blockers.[17] Perhaps this is due to population differences, ours being entirely female and somewhat older (mean age 66 years vs. mean age 59 years), and with chronic stable CAD.

There are notable limitations to our study. Our confidence intervals do not exclude smaller effect sizes for SCD risk for the SNPs studied, though given the overall magnitude of SCD events they are sufficient to exclude moderate effect sizes. There is also the possibility that we may have missed a significant risk in ethnic and other substrata; however, analyses restricted to Caucasians showed very similar results as compared to those for the overall study. Differences in mean EF between SCD cases and the minority of CAD controls in whom EF was available may be due to differences in timing of EF determination (peri-arrest vs. 1–3 months after MI). We may also have missed an effect of an unexamined genotype in LD with

our SNPs. Finally, only 80% of the overall HERS cohort and 50% of HERS participants suffering SCD were available for genetic analyses primarily due to inability to obtain surrogate consent. While this may be a source of potential bias, it is highly unlikely that subjects' genotypes would be associated with an inability to obtain consent.

The strengths of our study include the rigorously phenotyped and adjudicated SCD cases and outcomes of SCD and NFVA, and the comparison to a background of known CAD in two diverse populations. Different designs by different investigators studying different populations produced null results with similar confidence intervals.

Conclusion

In summary, our results suggest that these functional β1AR and β2AR polymorphisms are not substantial risk factors for SCD associated with CAD. Risk for complex traits such as SCD in the setting of CAD are expected to be the summation of genetic, epigenetic, and environmental effects. As replication of genetic association studies is key, the contrasting findings of this study and prior reports of similar population sizes call into question the role for these common βAR SNPs in the risk of SCD related to CAD. Examination of these SNPs in combination with other candidate gene SNPs and in other populations may clarify this disparity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary of Abbreviations

SNP
: single nucleotide polymorphism

LD
: linkage disequilibrium

βAR
: β adrenergic receptor

VA
: ventricular arrhythmia

NFVA
: nonfatal ventricular arrhythmia

VT
: ventricular tachycardia

VF
: ventricular fibrillation

SCD

sudden cardiac death

ICD
implantable cardioverter-defibrillator

HERS
Heart and Estrogen Replacement Study

EF
ejection fraction

CAD
coronary artery disease

MI
myocardial infarction

CHF
congestive heart failure

ACS
acute coronary syndrome

PTCA
percutaneous transluminal coronary angioplasty

CABG
coronary artery bypass graft

OR
odds ratio

RR
relative risk

CI
confidence interval

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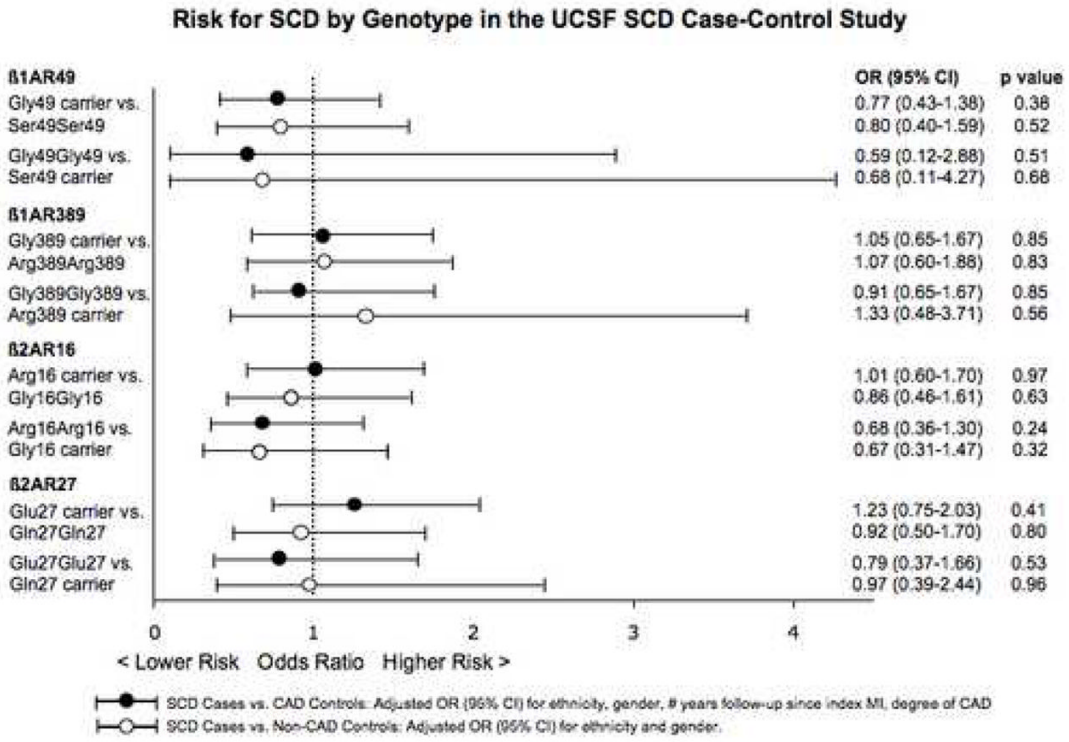

Figure 1.
Risk for SCD by Genotype in the UCSF SCD Case-Control Study

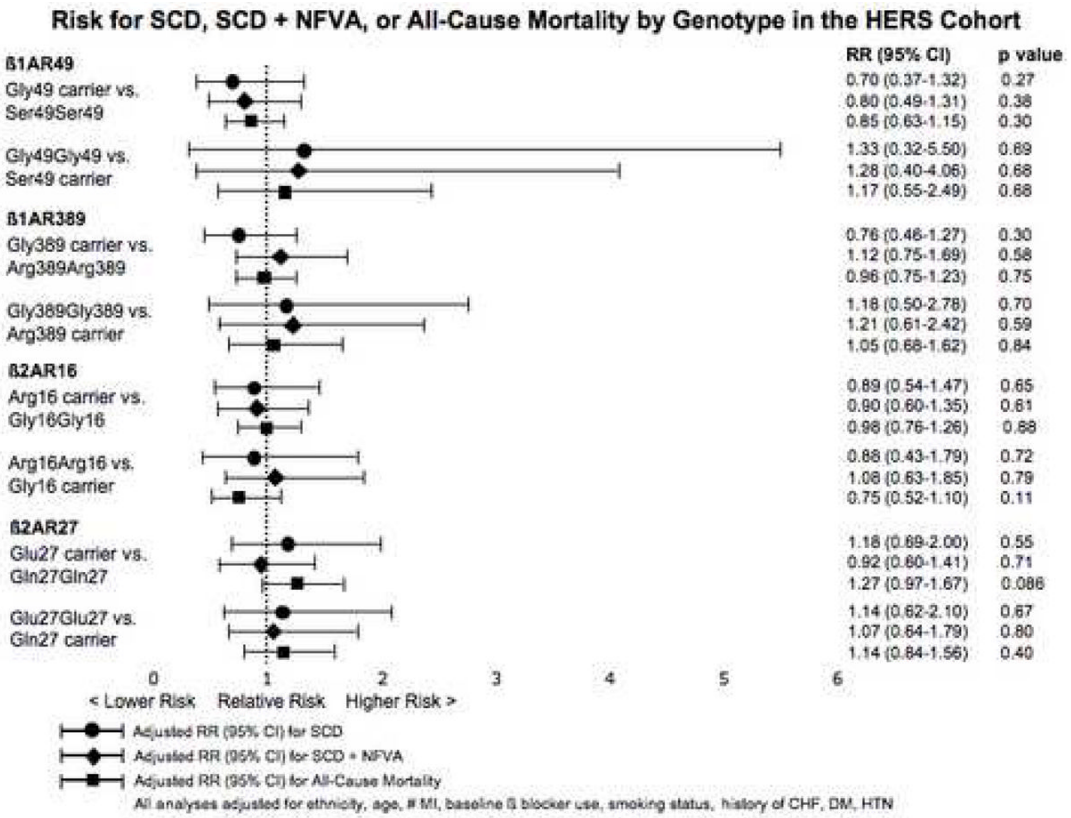

Figure 2.
Risk for SCD, SCD + NFVA, and All-Cause Mortality by Genotype in the HERS Cohort

Heart Rhythm. Author manuscript; available in PMC 2009 September 14.

Table 1

Baseline Characteristics of UCSF SCD Case-Control Study

Characteristic	All SCD Cases (n= 107)	CAD Controls (n= 287)	P value*	Non-CAD Controls (n= 101)	P value*
Male (%)**	92 (86.0%)	243 (84.7%)	0.75	90 (89.1%)	0.50
Ethnicity (%)**			0.87		0.84
White	82 (76.6%)	213 (74.2%)		78 (77.2%)	
Black	5 (4.7%)	21 (7.3%)		7 (6.9%)	
Asian	11 (10.3%)	33 (11.5%)		10 (9.9%)	
Hispanic	6 (5.6%)	14 (4.9%)		5 (5.0%)	
Other	3 (2.8%)	6 (2.1%)		1 (1.0%)	
Age at Index MI**	57.1 ± 14.2	57.1 ± 12.4	0.96	N/A	
Years of Follow Up since MI**	14.4 ± 9.0	14.5 ± 8.9	0.93	N/A	
Revascularization (%)**					
CABG	56 (52.3%)	142 (49.5%)	0.61	N/A	
Stent	35 (32.7%)	71 (24.7%)	0.29	N/A	
PTCA	12 (11.2%)	57 (19.9%)	0.12	N/A	
Diabetes (%)	15 (18.1%)	64 (22.4%)	0.40	12 (12.2%)	0.27
Current Smoker (%)	12 (14.6%)	18 (6.3%)	0.015	4 (4.1%)	0.013
BMI	25.9 ± 4.6	26.9 ± 5.1	0.11	25.4 ± 3.3	0.50
HTN (%)	58 (54.2%)	175 (61.0%)	0.22	0 (0%)	0.00
Medications					
β blocker	72 (67.3%)	147 (51.2%)	0.14	N/A	
ACE-I/ARB	55 (51.4%)	105 (36.6%)	0.057	N/A	
Statin	59 (55.1%)	166 (57.8%)	0.60	N/A	
Aspirin	74 (69.2%)	201 (70.0%)	0.95	N/A	

* from t-tests or chi-square tests for comparison with SCD cases

** variables matched on a group level between SCD cases and CAD controls

Table 2

Allele and Haplotype Frequencies in the UCSF SCD Case Control study

Allele/Haplotype	SCD Cases (all) n=107	CAD Controls (all) n=287	NonCAD Controls (all) n=101	SCD Cases (Caucasian) n=82	CAD Controls (Caucasian) n=213	NonCAD Controls (Caucasian) n=78
β2AR16						
Gly 16	58%	54.6%	53.7%	59.7%	57.2%	56.3%
Arg 16	42%	45.4%	46.3%	40.3%	42.8%	43.7%
β2AR27						
Gln 27	66.3%	67.7%	65.3%	60.1%	62%	59.7%
Glu 27	33.7%	32.3%	34.7%	39.9%	38%	40.3%
H1 (Gly16, Glu27)	34.0%	32.0%	34.2%	40.9%	37.4%	39.9%
H2 (Arg16, Gln27)	42.0%	44.9%	46.7%	40.3%	42.1%	44.2%
H3 (Gly16, Gln27)	24.0%	23.1%	19.0%	18.8%	20.5%	15.9%
β1AR49						
Ser49	89.3%	86.2%	86.7%	91.1%	86.8%	86.7%
Gly49	10.7%	13.8%	13.3%	8.9%	13.2%	13.3%
β1AR389						
Arg389	69.5%	69.7%	70.9%	69.4%	70.2%	70.7%
Gly389	30.5%	30.3%	29.1%	30.6%	29.8%	29.3%

Table 3

Table 3A: Baseline Characteristics of HERS Subjects by β1AR49 and β1AR389 Genotype

	β1AR49 Genotype (N=2172)				β1AR389 Genotype (N=2139)			
Characteristic	**Ser49/Ser49 (N=1641)**	**Ser49/Gly49 (N= 477)**	**Gly49/Gly49 (N= 54)**	**p value**	**Arg389/Arg389 (N=1124)**	**Arg389/Gly389 (N= 827)**	**Gly389/Gly389 (N= 188)**	**p value**
Age (years)	66.4 ± 6.6	66.5 ± 6.6	67.1 ± 6.2	0.73	66.6 ± 6.6	66.3 ± 6.6	66.1 ± 6.4	0.36
Race				0.63				<.0001
Caucasian	1500 (91.4%)	424 (88.9%)	46 (85.2%)		1049 (93.3%)	732 (88.5%)	157 (83.5%)	
Afr-Am	96 (5.9%)	38 (8.0%)	6 (11.1%)		41 (3.7%)	71 (8.6%)	27 (14.4%)	
Hispanic	26 (1.6%)	9 (1.9%)	2 (3.7%)		22 (2.0%)	12 (1.5%)	3 (1.6%)	
Other	19 (1.2%)	6 (1.3%)	0		12 (1.1%)	12 (1.5%)	1 (0.5%)	
Diabetes	357 (21.8%)	99 (20.8%)	9 (16.7%)	0.61	237 (21.1%)	180 (21.8%)	46 (24.6%)	0.55
Prior MI	843 (51.4%)	234 (49.1%)	27 (50.0%)	0.67	581 (51.7%)	422 (51.0%)	87 (46.3%)	0.39
Current smoker	190 (11.6%)	61 (12.8%)	8 (14.8%)	0.62	124 (11.0%)	107 (12.9%)	23 (12.2%)	0.43
History of CHF	191 (11.6%)	54 (11.3%)	3 (5.6%)	0.38	121 (10.8%)	103 (12.5%)	24 (12.8%)	0.45
On β blocker at baseline	538 (32.8%)	159 (33.3%)	20 (37.0%)	0.80	382 (34.0%)	265 (32.0%)	58 (30.9%)	0.54
Hypertension	563 (34.3%)	160 (33.5%)	18 (33.3%)	0.95	394 (35.1%)	284 (34.3%)	50 (26.6%)	0.075

Table 3B: Baseline Characteristics of HERS Subjects by β2AR16 and β2AR27 Genotype

	β2AR16 Genotype (N=2134)				β2AR27 Genotype (N=2129)			
Characteristic	**Gly16/Gly16 (N= 837)**	**Gly16/Arg16 (N= 989)**	**Arg16/Arg16 (N= 308)**	**p value**	**Gln27/Gln27 (N= 742)**	**Gln27/Glu27 (N=1010)**	**Glu27/Glu27 (N= 377)**	**p value**
Age (years)	66.5 ± 6.7	66.5 ± 6.5	66.4 ± 6.6	0.97	66.3 ± 6.6	66.4 ± 6.5	67.0 ± 6.6	0.28
Race				<.0001				<.0001
Caucasian	779 (93.1%)	887 (89.7%)	267 (86.7%)		624 (84.1%)	938 (92.9%)	364 (96.6%)	
Afr-Am	41 (4.9%)	74 (7.5%)	24 (7.8%)		74 (10.0%)	58 (5.7%)	9 (2.4%)	
Hispanic	12 (1.4%)	21 (2.1%)	4 (1.3%)		23 (3.1%)	12 (1.2%)	2 (0.5%)	
Other	5 (0.6%)	7 (0.7%)	13 (4.2%)		21 (2.8%)	2 (0.2%)	2 (0.5%)	
Diabetes	166 (19.9%)	226 (22.9%)	72 (23.5%)	0.22	164 (22.1%)	224 (22.2%)	75 (20.0%)	0.64
Prior MI	419 (50.1%)	505 (51.1%)	168 (54.6%)	0.40	389 (52.4%)	509 (50.4%)	188 (49.9%)	0.62
Current smoker	103 (12.3%)	121 (12.2%)	37 (12.0%)	0.99	92 (12.4%)	122 (12.1%)	44 (11.7%)	0.94
History of CHF	89 (10.6%)	117 (11.8%)	41 (13.3%)	0.43	88 (11.9%)	124 (12.3%)	35 (9.3%)	0.29

Table 3B: Baseline Characteristics of HERS Subjects by β2AR16 and β2AR27 Genotype

	β2AR16 Genotype (N=2134)				β2AR27 Genotype (N=2129)			
Characteristic	**Gly16/Gly16 (N= 837)**	**Gly16/Arg16 (N= 989)**	**Arg16/Arg16 (N= 308)**	**p value**	**Gln27/Gln27 (N= 742)**	**Gln27/Glu27 (N=1010)**	**Glu27/Glu27 (N= 377)**	**p value**
On β blocker at baseline	275 (32.9%)	326 (33.0%)	100 (32.5%)	0.99	245 (33.0%)	336 (33.3%)	121 (32.1%)	0.92
Hypertension	293 (35.0%)	335 (33.9%)	108 (35.1%)	0.86	240 (32.4%)	349 (34.5%)	135 (35.8%)	0.45

Table 4

Allele and Haplotype Frequencies in the Genotyped HERS Cohort:

Allele/Haplotype	HERS (overall) n=2199	HERS (Caucasian) n=1994	HERS (African-Am) n=143
β2AR16			
Gly 16	62.4%	63.2%	56.5%
Arg 16	37.6%	36.8%	43.5%
β2AR27			
Gln27	58.6%	56.7%	73%
Glu27	41.4%	43.2%	27%
H1 (Gly16, Glu27)	41.4%	43.4%	25.7%
H2 (Arg16, Gln27)	37.6%	36.7%	43.8%
H3 (Gly16, Gln27)	21.0%	19.9%	30.4%
β1AR49			
Ser49	86.5%	86.9%	82.1%
Gly49	13.5%	13.1%	17.9%
β1AR389			
Arg389	71.9%	73%	55%
Gly389	28.1%	27%	45%