β2-Adrenergic Receptor Genetic Variants and Risk of Sudden Cardiac Death

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Background—Sympathetic activation influences the risk of ventricular arrhythmias and sudden cardiac death (SCD), mediated in part by the β2-adrenergic receptor (B2AR). We investigated whether variation in the B2AR gene is associated with SCD risk.

Methods and Results—In this study, 4441 white and 808 black Cardiovascular Health Study (CHS) participants were followed up prospectively for SCD and genotyped for B2AR Gly16Arg and Gln27Glu polymorphisms. The study was replicated in 155 case and 144 control white subjects in a population-based case-control study of SCD, the Cardiac Arrest Blood Study (CABS). In CHS, Gly16 and Gln27 allele frequencies were 62.4% and 57.1% among white and 50.1% and 81.4% among black participants. Over a median follow-up of 11.1 years, 156 and 39 SCD events occurred in white and black participants, respectively. The Gln27Glu variant was associated with SCD risk (P = 0.008 for general model). SCD risk was higher in Gln27 homozygous participants than in Glu27 carriers (ethnicity-adjusted hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.17 to 2.09; P = 0.003). The increased risk did not differ significantly between white (HR, 1.62; 95% CI, 1.18 to 2.23) and black (HR, 1.23; 95% CI, 0.61 to 2.48) participants, although the confidence interval was wide in blacks. In the CABS replication study, Gln27 homozygous participants similarly had higher SCD risk than Glu27 carriers (odds ratio, 1.64; 95% CI, 1.02 to 2.63; P = 0.040). Gly16Arg was not associated with SCD risk in either study.

Conclusions—Gln27 homozygous individuals have an increased risk of SCD in 2 study populations. Our findings suggest that B2AR plays a role in SCD in humans. Study of genetic variation within the B2AR gene may help identify those at increased SCD risk. (Circulation. 2006;113:1842-1848.)

Key Words: death, sudden ■ epidemiology ■ genetics ■ receptors, adrenergic, beta

Sudden cardiac death (SCD) accounts for 450 000 deaths in the United States each year.1 SCD and ventricular arrhythmias have been associated with cardiac sympathetic activation and higher cardiac and serum norepinephrine levels.2-4 Animal studies suggest that the β2-adrenergic receptor (B2AR) partly mediates this response to sympathetic activation.5,6 A family history of SCD is associated with a doubled SCD risk, suggesting a genetic susceptibility.7 Whether genetic variation in the B2AR gene is associated with SCD risk in humans has not previously been explored.

B2AR is a small intronless gene. Thirteen single nucleotide polymorphisms (SNPs) have been described that are in linkage disequilibrium.8 Two common SNPs result in the amino acid substitutions Gly16Arg and Gln27Glu. In transfected cell lines, these amino-terminus SNPs alter cellular trafficking of the receptor protein, resulting in variation in agonist-promoted receptor downregulation.9 These 2 variants are in strong linkage disequilibrium; Glu27 almost always is paired with Gly16 in humans. Therefore, 3 common haplotypes exist: H1 (Gly16-Glu27), H2 (Arg16-Gln27), and H3 (Gly16-Gln27).9 Because the disease association of a SNP...
may depend on its cis interactions with other SNPs in a gene, we examined haplotypes in addition to individual SNPs. To investigate whether functional variants of the B2AR gene influence SCD risk, we genotyped 5249 elderly individuals who were followed up prospectively to identify SCD events. We validated the findings in a population-based case-control study of SCD.

Methods

Study Populations

Cardiovascular Health Study

The Cardiovascular Health Study (CHS) is a population-based prospective cohort study of cardiovascular disease in the elderly. In 1989 to 1990 and 1992 to 1993, 4 field centers recruited 5888 participants ≥65 years of age from Medicare eligibility lists. Individuals were excluded if they were unable to participate in the baseline examination or were not expected to return for the 3-year follow-up. Details of the CHS study design and participant recruitment are described elsewhere.10 For this analysis, participants were excluded if they did not have DNA available (n = 213), did not consent to use of their genetic information (n = 273), were missing genotype data (n = 114), or did not self-identify as white or black (n = 39), leaving 4441 white and 808 black participants.

Participants underwent annual evaluations that included assessment of cardiovascular risk factors, comorbidities, and clinical and laboratory measurements. Comprehensive data were gathered on cardiovascular events and deaths from hospital records, interviews with physicians, next of kin and/or witnesses, death certificates, and autopsy reports. Cause of death and nonfatal myocardial infarctions were adjudicated by committee.11 This analysis included events occurring by June 30, 2001, from the updated CHS database. SCD was operationally defined as a sudden pulseless condition from a cardiac origin in a previously stable individual occurring out of hospital or in the emergency room. By definition, SCD cases could not have a life-threatening noncardiac cause. SCD cases were 25 to 74 years of age and were not residents of a nursing home, to avoid misclassification as to cause of death. Furthermore, cases were restricted to married individuals to obtain spousal information on risk factors and comorbidities. The spouses of ~85% of eligible case patients agreed to participate in an in-person interview. Control subjects, matched to cases in age and sex with the same eligibility criteria, were randomly selected from the community by random-digit dialing. Spouses completed a questionnaire on comorbidities and cardiac risk factors for case and control subjects. Details of the CHS recruitment experience are described elsewhere.12 We further restricted our present study of genetic variants to white participants, because we had too few participants of other ethnicity to perform meaningful analyses. A sample of 155 case and 144 control white subjects with DNA available was genotyped for B2AR gene variants.

For both studies, institutional review board approval was obtained, and study subjects and/or spouses (CABS) provided informed consent.

SNP Selection and Genotyping

Common variants of the B2AR gene were identified from complete sequence information obtained by Drysdale et al8 in 23 whites and 19 blacks. In whites, this number of individuals allows for >99% probability of identifying a variant with an allele frequency of ≥5%.13 Of the 12 haplotypes identified, only 3 were common in whites, accounting for 95% of the haplotypes seen in this population.8 A haplotype tree of these 3 common haplotypes was constructed with the MEGA program based on the number of differences between haplotypes by UPGMA clustering method (Figure 1).14 We selected 2 informative variants, Gly16Arg and Gln27Glu, that differentiate the 3 common haplotypes defined by Gly16-Glu27, Arg16-Gln27, and Gln16-Gln27. Among blacks, 3 haplotypes account for >95% of the variation seen in the coding and promoter regions of the B2AR gene. The Arg16-Gln27 allele is further differentiated into 2 haplotypes, both common in blacks, by SNPs in upstream regions at nucleotide positions −1023 and −654.15 The Thr164His variant was not examined because it is rare (allele frequency, 1% to 2% in whites and blacks); its effect on SCD risk would have to be large for our study to have adequate power to detect an association.

Details of the blood collection protocol and sample storage for CHS and CABS are described elsewhere.10,15 In CHS, unphased genotyping of the B2AR gene was performed after PCR amplification using 2 methods. Initially, the Gly16Arg and Gln27Glu variants were detected on a subset of 2166 participants using 2 restriction enzyme digestions. Genotyping was completed on the remainder of the cohort using a high-throughput TaqMan assay (Applied Biosystems, Foster City, Calif).16 Both methods were used to genotype a sample of 222 subjects representing all diplotype (ie, haplotype pairs) with 99.6% intermethod agreement and 96% reproducibility. The findings in a population-based case-control study of SCD.

Figure 1. Haplotype tree of the B2AR gene. Ten SNPs differ between the 3 common haplotypes. Two evolutionary distant clades are identified that completely segregate at 6 SNPs (italics). Gln27Glu (bold, italics) tags the first clade, which contains only the H1 haplotype. Arg16Gly (bold) differentiates the H2 and H3 haplotypes in the second clade. A variant in the leader cistron (LC) region of the B2AR gene, Cys19Arg, is found only in the H1 haplotype. The remaining SNPs either are in noncoding regions or are synonymous.8
agreement. In CABS, unphased genotyping was performed using direct sequencing after PCR amplification. Oligonucleotide primers were designed to amplify the coding sequence of B2AR to include SNPs for both Arg16Gly and Gln27Glu in a single amplicon. The PCR product was sequenced using big dye terminator chemistry and an ABI310 DNA sequencer. All genotyping was performed by researchers blinded to outcome.

To investigate the potential for population admixture, 4 markers were examined in the full CHS cohort (apolipoprotein E alleles 2, 3, and 4; angiotensin type I receptor C1166A SNP; aducin Gly460Tnp SNP) or partial cohort (all blacks and one third of the whites, G-protein β-subunit C825T SNP) using restriction-fragment-length polymorphism and/or TaqMan allelic discrimination system on the basis of protocols detailed elsewhere.18–21

Statistical Analyses

Hardy-Weinberg equilibrium was assessed by χ² test. Haplotypes and their frequencies were estimated from genotypes by the expectation maximization method using the Arlequin program (University of Geneva, Geneva, Switzerland).22 Differences in participant characteristics by genotype were assessed with χ² and Student’s t tests. In CHS, the genotype-SCD association was assessed using the Cox proportional hazards regression model with age as the time axis. The overall association of genotype with SCD risk was assessed using Cox regression with indicator variables representing the heterozygous and each of the respective homozygous genotypes. For the SNP (Gln27Glu) and haplotype (H1) with significant effects, we then assessed autosomal dominant, recessive, and additive models. Nested models were compared by likelihood ratio tests. Conservative likelihood ratio tests were done for nonnested models using critical values appropriate for a larger and blacks (OR, 1.00; 95% CI, 0.73 to 1.37). Non-SCD atherosclerotic deaths occurred in white and 280 in black subjects. Gln27 Glu27 carriers among whites (OR, 1.06; 95% CI, 0.93 to 1.20) than in participants with Glu27 homozygous participants had the same risk of total mortality as participants with ≥1 Glu27 alleles (ethnicity adjusted hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.17 to 2.09) (Table 3). This increased SCD risk did not differ significantly between white (HR, 1.62; 95% CI, 1.18 to 2.23) and black (HR, 1.23; 95% CI, 0.61 to 2.48) participants (interaction P=0.48), although the CI was wide and crossed 1.0 in blacks. Adjustment for ethnicity, age, gender, clinic site, smoking status, and history of myocardial infarction, congestive heart failure, diabetes, and hypertension at study entry did not affect this association (adjusted HR, 1.50; 95% CI, 1.12 to 2.00). The association of SCD with genotype was not notably different in subgroups defined by these covariates (interaction P>0.10 for all comparisons).

To determine whether the association was influenced by survival bias, the risks of total mortality and mortality by cause of death were compared by genotype. During follow-up, 1838 deaths occurred in white and 280 in black subjects. Gln27 homozygous participants had the same risk of total mortality as Glu27 carriers among whites (OR, 1.06; 95% CI, 0.93 to 1.20) and blacks (OR, 1.00; 95% CI, 0.73 to 1.37). Non-SCD atherosclerotic death and noncardiac death risk were not associated with genotype.

We further examined the association of the B2AR Gln27Glu variant with other ischemic heart disease events among whites. Compared with Glu27 carriers, Gln27Gln27 participants did not have a significantly increased risk of nonfatal myocardial infarctions (n=384 non-fatal myocardial infarctions; HR, 1.17; 95% CI, 0.95 to 1.44) or non-SCD atherosclerotic deaths (n=345 deaths; HR, 0.90; 95% CI, 0.71 to 1.13), suggesting that this variant may play a role in SCD specifically rather than in ischemic heart disease in general.

The possibility that genetic admixture could have resulted in a spurious association among white participants was explored by several methods. First, 4 polymorphic markers (apolipoprotein E

### Results

**CHS: SNP Analysis**

Gly16Arg and Gln27Glu were in Hardy-Weinberg equilibrium in both white and black participants. The 2 SNPs were in strong linkage disequilibrium, resulting in 3 common haplotypes (Table 1). SNP and haplotype frequencies differed between the 4441 white and 808 black study participants (P<0.001). Within each ethnicity, there were no significant differences by genotype in baseline characteristics (Table 2).

Over the median follow-up of 11.2 and 8.2 years, 156 and 39 SCD events occurred in white and black subjects, respectively.

| TABLE 1. B2AR Gene Polymorphism Allele Frequencies and Haplotype Structure and Frequency in White and Black CHS Participants and White CABS Control Subjects |
|-----------------|-----------------|-----------------|
|                 | CHS, %          | CABS, %         |
|                 | White Participants | Black Participants | White Control Subjects |
| Codon 16 polymorphism |                 |                 |
| Gly16           | 62.4            | 50.1            |
| Arg16           | 37.6            | 49.9            |
| Codon 27 polymorphism |               |                 |
| Gln27           | 57.1            | 81.4            |
| Glu27           | 42.9            | 18.6            |
| Haplotype*      |                 |                 |
| H1 (Gly16-Glu27) | 42.9            | 18.6            |
| H2 (Arg16-Gln27)| 37.6            | 49.9            |
| H3 (Gly16-Gln27)| 19.5            | 31.5            |

*A single white CHS participant had an H4 Arg16-Glu27 haplotype, yielding a haplotype frequency of 0.0001%.*
alleles 2, 3, and 4; angiotensin type 1 receptor C1166A SNP; adducin Gly460Trp SNP; and G-protein \( \beta \)/H9252-subunit C825T SNP) were genotyped. Allele frequencies for all 4 markers differed between CHS white and black subjects (\( P = 0.001 \)). Among whites, there were no significant differences in the frequencies of these markers by B2AR genotype and no association of these markers with SCD risk (all \( P > 0.15 \)), suggesting that admixture is less likely to account for our findings. Furthermore, adjusting for each of these markers did not change the association of SCD with B2AR variants. Second, the analysis was repeated, restricting the sample to each of the 4 clinic sites. The association in all 4 clinic sites was in the same direction (reaching statistical significance in 2 of 4 sites) and did not significantly differ between sites. Finally, we repeated these analyses in a second white study population (see CABS results below).

The Gly16Arg variant was not associated with SCD risk among white and black participants (\( P = 0.66 \)).

**CHS: Haplotype Analysis**

We next investigated whether the Gly16Arg and Gln27Glu variants in combination identified those at increased SCD risk. Because the Glu27 variant is found almost exclusively in the H1 haplotype, analyses of the H1 haplotype yielded results nearly identical to those obtained with the Glu27 variant. Participants who lack an H1 haplotype (Gln27 homozygous) had a higher SCD risk than H1 haplotype (Glu27) carriers (ethnicity-adjusted HR, 1.56; 95% CI, 1.17 to 2.09; \( P = 0.003 \)). The H2 (\( P = 0.66 \)) and H3 (\( P = 0.08 \)) haplotypes were not associated with SCD risk.

We further analyzed SCD risk among whites by diplotype. Compared with the most common diplotype, H1H2, SCD risk was not different in participants with either the H1H1 or H1H3 diplotype but was increased in participants without an H1 allele (H2H3, H2H2, and H3H3) (Figure 2). This is consistent with our SNP and haplotype analyses, which suggest that Gln27 homozy-

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<th>TABLE 2. Baseline Characteristics of 4441 White and 808 Black CHS Participants by Gln27Glu Genotype</th>
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For each ethnic group, there were no significant differences in baseline characteristics by genotype (all \( P > 0.05 \)).

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<th>TABLE 3. Risk of SCD Among All CHS Participants (Adjusted for Ethnicity) and in Whites and Blacks According to Gln27Glu Genotype</th>
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<td><strong>Genotype</strong></td>
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Ref indicates reference.

*Incidence rate per 1000 person-years.
†Glu27 carrier has either 1 or 2 copies of the Glu27 allele.
‡NS = \( P > 0.05 \).
gous (H2H2, H2H3, H3H3) individuals are at higher risk than Glu27 carriers (H1H1, H1H2, H1H3).

CABS
To validate these initial results, we replicated the study in a population-based case-control study of SCD. Traditional risk factors of hypertension and smoking status were more prevalent among the 155 cases than the 144 controls (Table 4). Given the sampling, mean age and sex distribution were similar in cases and controls. All subjects were white. Among controls, Gly16Arg and Gln27Glu were in Hardy-Weinberg equilibrium, and allele frequencies were similar to those found among CHS whites (Table 1).

Similar to the findings in CHS, the odds of SCD were higher in Gln27 homozygous CABS subjects (those without the H1 haplotype) than in Glu27 carriers (OR, 1.64; 95% CI, 1.02 to 2.63; \( P \approx 0.040 \), adjusted for the sampling variables of age, sex, and index year). This association remained after further adjustment for cardiovascular risk factors of hypertension, diabetes, and smoking status (adjusted OR, 1.83; 95% CI, 1.11 to 3.04).

The Gly16Arg variant (\( P \approx 0.25 \)) and the H2 (\( P \approx 0.25 \)) and H3 (\( P \approx 0.65 \)) haplotypes were not associated with SCD risk.

Discussion
The results of this study show that specific common B2AR genetic variants are associated with increased risk of SCD. In a prospective study (CHS), Gln27 homozygous participants had a 58% higher SCD risk than participants with \( \geq 1 \) Glu27 alleles (ethnicity-adjusted HR, 1.56; 95% CI, 1.17 to 2.09). This increased SCD risk did not differ significantly between white (HR, 1.62; 95% CI, 1.18 to 2.23) and black (HR, 1.23; 95% CI, 0.61 to 2.48) participants, although the confidence interval was wide in blacks. The study was replicated in a separate population-based case-control study of cardiac arrest in which Gln27 homozygous individuals had a 64% higher risk of SCD among whites (OR, 1.64; 95% CI, 1.02 to 2.63).

We investigated this gene as a candidate risk factor for SCD because of basic and clinical studies suggesting that B2AR may play an important role in SCD. In ischemic dog models, selectively blocking B2AR prevents ventricular fibrillation. Treatment with nonselective \( \beta \)-blockers (that block both the \( \beta_1 \)- and \( \beta_2 \)-adrenergic receptors) decreases SCD incidence in randomized clinical trials\(^6\) and may be associated with lower SCD incidence than treatment with \( \beta_1 \)-selective agents alone\(^24,25\), underscoring the importance of B2AR in SCD. Our findings provide support that the B2AR plays a role in SCD in humans.

The B2AR haplotypes are evolutionarily distant and functionally different. In transfected cell lines, these molecular haplotypes defined by the amino-terminus SNPs lead to differential agonist-promoted receptor downregulation.\(^9\) A variant in the leader cistron, Cys19Arg, found primarily in the H1 (Gly16-Glu27) haplotype, alters receptor translation, hence affecting B2AR protein expression.\(^8\) Human beings with varying B2AR alleles respond differently to administration of \( \beta \)-adrenergic agonists.\(^26\)

In the heart, B2AR is located on the myocardium and presynaptically on sympathetic nerve terminals.\(^27\) Presynaptic B2AR stimulation upregulates cardiac norepinephrine release. Sympathetic activation and higher serum norepinephrine levels are associated with SCD and ventricular fibrillation.\(^2,4,27,28\) On cardiac cells, B2AR activation modulates cardiac chronotropy, inotropy, and ion channel function.\(^6,29,30\) Higher heart rate, the presence of heart failure, and abnormal ion channel function are risk factors for SCD.\(^31-33\) Variability in response to \( \beta_2 \)-adrenergic stimulation resulting from receptor allelic differences may account for our findings.

B2AR also is located on a number of noncardiac tissues, including vasculature, lung parenchyma, adipocytes, and platelets; its effects on these tissues may influence SCD risk. For instance, in adipocytes, catecholamine stimulation leads to lipolysis and release of nonesterified fatty acids. Higher nonesterified fatty acid levels are associated with ventricular ectopy and SCD.\(^34\) In a sibling study, Gln27 was associated with higher nonesterified fatty acid levels, consistent with our finding that Gln27 is associated with higher risk of SCD.\(^35\)

The association of these common B2AR variants with other SCD risk factors such as diabetes, hypertension, myocardial
infarction, and heart failure have been examined in prior studies, and consistent associations have not been found.35–38 The present study showed no association of B2AR variants with these SCD risk factors at study entry.

Previously, we showed in CHS that Gln27 homozygous participants had a higher risk of coronary events (combined nonfatal and fatal myocardial infarction and coronary death) compared with Glu27 carriers.39 In the present study, we hypothesized that B2AR variants would be associated with SCD in particular and carefully classified all cardiac deaths in CHS for the occurrence of SCD. Nineteen percent (n=133) of the coronary event cases in our previous report had SCD and are included in the present analysis of SCD. In this analysis, Gln27 is associated with increased risk of SCD but not with nonsudden atherosclerotic death, suggesting that this variant may play a role in fatal arrhythmia specifically rather than in ischemic heart disease in general.

Several limitations to the interpretation of our findings deserve consideration. First, although both are population based, the design of and populations in the 2 studies differ. CHS is a cohort study of older adults with and without heart disease at baseline. In contrast, CABS is a case-control study of younger adults without clinically recognized heart disease. Because of these eligibility restrictions in the CABS study, a large proportion of SCD events in Seattle and King County were not included. Nonetheless, the similar associations observed in the 2 studies suggest that the association of genetic variation in the B2AR gene with SCD risk is present in different populations. Moreover, these studies were performed in white and black adults. The findings among whites may not be generalizable to other ethnic groups. Moreover, because of low Gln27 allele frequency and few SCD events, we had limited power to detect an association in blacks. Additionally, population admixture is a potential concern with genetic association studies. To minimize this problem, the analyses were stratified by ethnicity. Furthermore, among whites, the 4 unrelated markers examined showed similar allele frequencies by B2AR genotype, suggesting that there was not unequal genetic admixture in the groups. However, fine population stratification that may result in a spurious association cannot be excluded. Importantly, 2 different white populations showed similar findings. Conditions that permit major bias are unlikely to be repeated in a second population.40 In summary, this is the first study to demonstrate an association of a common functionally important genetic variant with SCD in a large cohort followed up prospectively and to replicate the findings in a second population. SCD is common, accounting for 10% of all adult deaths.41 It frequently presents as the first and only manifestation of previously unrecognized ischemic heart disease. Identifying those at increased risk remains a public health challenge. The findings of this investigation suggest that common genetic markers may help identify those at increased risk of SCD in the general population and support the need for further investigation of genomic variation in the B2AR gene. Additionally, larger studies are needed to assess more fully the potential interactions with modulators of the adrenergic nervous system such as exercise, stress, and treatment with β-blocking medications. Ultimately, the goal of these studies is to improve risk stratification and the identification of those who may benefit from preventive measures.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Sudden cardiac death (SCD) is a major public health concern, accounting for 450 000 deaths in the United States each year. It frequently presents as the first and only manifestation of previously unrecognized ischemic heart disease. Identifying those at increased risk remains a public health challenge. In 2 study populations, we show that individuals who are homozygous for the Gln27 allele of the β2-adrenergic receptor (B2AR) gene are at ~60% increased risk of SCD. The findings of this investigation suggest that common genetic markers may help identify those at increased risk of SCD in the general population and support the need for further investigation of genomic variation in the B2AR gene. Additionally, larger studies are needed to more fully assess potential interactions with modulators of the adrenergic nervous system such as exercise, stress, and treatment with β-blocking medications. Ultimately, the goal of these studies is to improve risk stratification and the identification of those who may benefit from preventive measures.
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