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In the Wrong Place with the Wrong SNP: The Association between Stressful Neighborhoods and Cardiac Arrest within Beta-2-Adrenergic Receptor Variants

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Abstract

Background—Sudden cardiac arrest has been linked independently both to stressful neighborhood conditions and to polymorphisms in the *ADRB2* gene. The *ADRB2* gene mediates sympathetic activation in response to stress. Therefore, if neighborhood conditions cause cardiac arrest through the stress pathway, the *ADRB2* variant may modify the association between neighborhood conditions such as socioeconomic deprivation and incidence of cardiac arrest.

Methods—The Cardiac Arrest Blood Study Repository is a population-based repository of specimens and other data from adult cardiac arrest patients residing in King County, Washington. Cases (n = 1,539) were 25- to 100-year-old individuals of European descent who experienced out-of-hospital cardiac arrest from 1988 to 2004. Interactions between neighborhood conditions and the *ADRB2* genotype on cardiac arrest risk were assessed in a case-only study design. Gene–environment independence was assessed in blood samples obtained from King County residents initially contacted by random-digit dialing.

Results—Fewer than 4% of study subjects resided in socioeconomically deprived neighborhoods. Nonetheless, the case-only analysis indicated the presence of supra-multiplicative

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interaction of socioeconomic deprivation and the homozygous Gln27Glu variant [Case-only odds ratio (OR): 1.8 (95% confidence interval [CI]: 1.0, 2.9)]. Interactions between population density and the homozygous Gln27Glu variant were weaker [Case-only OR: 1.2, (95% CI: 0.97, 1.5)].

Conclusions—Findings support a supra-multiplicative interaction between the Gln27Glu *ADRB2* variant and socioeconomic deprivation among individuals of European descent. This result is consistent with the hypothesis that the elevation in cardiac arrest risk associated with socioeconomic deprivation operates through the stress pathway.

Sudden cardiac arrest is a leading cause of death in the United States, resulting in about 450,000 deaths each year, [1,2] particularly in lower socio-economic status neighborhoods.[3,4]

Prior studies have suggested that stress may be a key risk factor for sudden cardiac arrest.[5–7] Sympathetic activation of the autonomic nervous system in response to stress increases synthesis and release of catecholamines through the opening of calcium channels in order to maintain homeostatic conditions; constant increases of catecholamines in turn induce arrhythmias and damage myocardial tissue.[6]

Residential neighborhood characteristics such as high population density and socioeconomic deprivation may be sources of stress. Overcrowded conditions have been associated with a stressful feeling of loss of control.[8] Neighborhood deprivation may cause stress through greater barriers to and competition for resources or through perceptions of lack of control or perceived threat.[4,9] More broadly, recent developments in brain imaging suggest that living in urban conditions may result in a neurologically different response to stressors.[10]

Genetics, particularly the Beta-2 Adrenergic Receptor *(ADRB2)* gene, may also play a role in the etiology of sudden cardiac arrest.[11–15] Beta-2-adrenergic receptors are cell membrane binding sites involved in sympathetic activation, as in the physiological stress response.[16] These receptors are present throughout the ventricular myocardium; when activated, they elicit an electrical response to release catecholamines and create disturbances in the membrane potential of myocardial cells by initiating the acceptance of more cytosolic calcium. Because a calcium ion balance is needed to facilitate normal heart rhythms and blood flow, the provoked electrical imbalance stimulates cardiac arrhythmias.[6,16] Recent studies have found elevated sudden cardiac arrest risk in subjects in three distinct populations whose single nucleotide polymorphism (SNP) at rs1042714 results in the Gln27Glu substitution in *ARDB2*,[14,15] though another study failed to replicate the association.[17]

Since variations in *ADRB2* may affect physiologic response to environmental stressors, the elevation in risk of sudden cardiac arrest associated with exposure to such stressors, including neighborhood conditions, may be modified by the *ADRB2* variant. Identification of such gene–environment interactions can help in targeting interventions to the individuals most vulnerable to harm from environmental exposures.[18] However, to the best of our knowledge, no previous research has examined the interaction of neighborhood conditions and *ADRB2* variants in risk of sudden cardiac arrest.

In this analysis, we investigate the interaction between variants in *ADRB2* and neighborhood conditions using a case-only approach. The Gln27Glu SNP is of primary interest because of previous findings of elevated sudden cardiac arrest risk among those homozygous for Gln27.[14] We hypothesized that greater socioeconomic deprivation and higher population density would be associated with those homozygous for Gln27 in cases but not in a population based sample of controls. However, Gln27Glu is in strong linkage disequilibrium with the Gly16Arg variant, such that 3 common haplotypes exist in humans: H1 (Gly16-Glu27), H2 (Arg16-Gln27), and H3 (Gly16-Gln27).[19] Because these SNPs may interact within the gene, we supplemented our primary analysis with a diplotype analysis to rule out the appearance of risk elevation due to Gln27Glu arising as an artifact of a true causal effect of Gly16Arg.

METHODS

Sample

Sudden cardiac arrest cases were selected from the population-based Cardiac Arrest Blood Study – Repository (CABS-R), a repository of data and specimens from patients with out-of-hospital cardiac arrest in Seattle and greater King County, Washington, between October 1988 and December 2004.[7,14,20] Blood specimens were collected from sudden cardiac arrest cases older than 18 years of age by attending paramedics. In the repository, sudden cardiac arrest was defined as an event resulting in a sudden, pulseless condition in an apparently otherwise stable person in the absence of a non-cardiac cause of arrest.

The records of 5,552 individuals identified by paramedics to be in cardiac arrest were reviewed and classified as definite, probable, or possible sudden cardiac arrest based on initial rhythm (ventricular fibrillation or asystole), circumstances (e.g. witnessed or unwitnessed), and possible contribution of comorbidities to the event. Cases were restricted to those with a cardiac arrest classified as definite or probable and with a presenting rhythm of ventricular fibrillation or asystole. We excluded nursing home residents because we expected they would not be subject to the same neighborhood environment influences that other subjects were.

Population-based controls were previously identified by random-digit dialing as part of the Diet and Primary Cardiac Arrest Study.[20] These controls were individually matched to a subset of CABS-R cases without diagnosed heart disease before their sudden cardiac arrest, based on sex and age (within seven years). CABS-R staff performed home interviews with all individuals who met these criteria and agreed to participate in the study. The overall control response rate was 64%.

Owing to the small number of racial or ethnic minority residents of King County, most CABS-R subjects are of European descent. To minimize biases due to population stratification, the present analysis was restricted to subjects of European descent. Study subjects missing genotype (n = 70), whose home address could not be geocoded (n=325), or whose home address was geocoded to a tract for which the US Census reported no housing units (n=49) were also excluded. The final sample included 1,539 cases (1,094 definite, 445 probable) and 480 controls.

The Human Subjects Review Committee at the University of Washington and Columbia University approved the study. All controls signed an informed consent form that included use of data and specimens for genetic studies. The use of repository data from the CABS-R for this study was authorized under a waiver of consent.

Environmental Variables

Home addresses of all subjects were geocoded to derive tract estimates from the 2000 US Census and tax assessor extracts. Subjects whose census tract was above the median measure per census tract in the sample (2,130 residents per square kilometer) were classified as living in a dense neighborhood. Subjects whose tract's median family income was less than 80% of the median King County family income in 2000, weighted for at least two family members ($40,150)[21], were classified as living in a socioeconomically deprived neighborhood.

Genotyping

Blood samples for cases were collected by paramedics in the field after emergency medical care was provided and the subject was clinically stable or declared dead. Blood samples for controls were collected by trained interviewers. Blood was collected in tubes containing EDTA, and white blood cells were separated from plasma and red blood cells through centrifugation and stored at −80C. DNA was extracted from the white blood cells of these specimens using standard phenol extraction procedures. Blood samples for cases and controls were subjected to identical processing methods and DNA extraction methods.

Genotyping for SNPs rs1042713 and rs1042714, corresponding to Arg16Gly and Gln27Glu, was performed in the laboratory of Dr Pui-Yan Kwok (Department of Biopharmaceutical Sciences, University of California, San Francisco, CA) using BeadArray tools with a custom GoldenGate panel (Illumina, San Diego, CA).[14,22]

Analyses

We used χ^2 tests to assess Hardy-Weinberg equilibrium.[23] For the primary single-SNP analyses, the homozygous Gln27 genotype ('CC') was designated as the high risk genotype owing to its previous association with sudden cardiac arrest risk.[14,15] For the diplotype analysis, H1H2 (i.e. one Gly16-Glu27 haplotype and one Arg16-Glu27 haplotype) acted as the reference group owing to its status as the most common diplotype. For both analyses, we used logistic regression to compute case-only odds ratios between the environmental exposures of interest and the genotype controlling for age at event and sex.

In the available data, cases have a high prevalence of prior clinically recognized cardiovascular disease whereas controls were selected to be free of clinically recognized disease. This difference in recruitment would likely result in strong selection bias in a conventional case-control analysis. We therefore used a case-only analysis,[24] in which the gene–environment odds ratio estimates the multiplicative interaction ratio of odds ratios that would have been observed in a case-control study.[24,25] Case-only studies also have greater power to detect multiplicative interactions compared to case–control studies;[25] this

efficiency benefit is particularly important for CABS-R, which is a case-focused registry with only a small sample of controls.

However, case-only analyses are valid only under the assumption of gene–environment independence in the general population.[24] To examine the gene–environment independence assumption, we computed adjusted and unadjusted control-only odds ratios using logistic regression. Because the Gln27 genotype is associated with only modest elevation of cardiovascular disease risk in the general population,[26] gene–environment association odds ratios observed in these controls should roughly approximate the odds ratios of the source population in spite of excluding those with clinically recognized disease.[27]

Finally, we performed three sensitivity analyses. First, to examine the sensitivity of our findings to our *a priori* definition of socioeconomic deprivation, we tested models in which neighborhoods were dichotomized at the sample median of median household income and at the sample median of median family income, and plotted kernel densities of median household income, median family income, housing vacancy rate, and population density by *ADRB2* status among cases and controls. Second, because all controls were 79 or younger, we tested the case-only analysis with cases limited to those aged 79 or less. Finally, to account for potential bias due to population stratification, we performed analyses adjusting for ethnic differences within our European descent population using the first five principal components identified by a principal component analyses of whole genome data as described by Price et al.[28] This analysis was limited to 1,443 cases owing to missing genome data for the remaining 576 subjects.

All analyses were performed using R for Windows Version 2.15.3 (Vienna, Austria).

RESULTS

Descriptive characteristics of the 1,539 cases and 480 controls and their home census tracts are presented in Table 1. Due to the selection procedures, sudden cardiac arrest cases were generally older than controls (median 71 years old among cases compared to 58 among controls). Both SNPs were in Hardy-Weinberg equilibrium in both cases and controls. Arg16Gly was in strong linkage disequilibrium with Gln27Glu ($D'=1.0$, $r^2=0.45$ in cases, $D'=1.0$, $r^2=0.49$ in controls). Slightly less than a third of the cases (31%) and controls (30%) were homozygous for the Gln27 genotype. Diplotypes were distributed similarly in cases and controls, with one H1 and one H2 haplotype most common (32% of cases and 35% of controls). Cases tended to live in census tracts with lower median family income (median $67,212 for cases compared to $72,045 for controls), more densely populated neighborhoods (2,273 residents/km^2 for cases compared to median 1,496 residents/km^2 for controls), and less floor space per housing unit (151 m^2 for cases' median compared to 173 m^2 for controls).

Table 2 displays results from case-only and control-only analyses. Results indicated supra-multiplicative interaction between high-risk Gln27Glu variant (homozygous Gln27) and socioeconomic deprivation (adjusted case-only OR 1.8, 95% CI 1.0, 2.9). The estimate of the hypothesized interaction between Gln27Glu variant and population density was more

modest (adjusted case-only OR 1.2, 95% CI 0.97, 1.5). Neither neighborhood exposure showed evidence of a positive association between the high-stress residential environment and the Gln27Glu variant in the controls.

We next investigated whether the Gly16Arg and Gln27Glu variants in combination interacted with neighborhood characteristics. This secondary analysis had less power to detect any interaction than the Gln27Glu analysis did; these resulting estimates were imprecise but consistent with the Gln27Glu variant acting as the relevant SNP (Table 3).

Sensitivity Analyses

Because very few of our subjects lived in neighborhoods categorized as socioeconomically deprived according to our *a priori* definition, we investigated the sensitivity of our observed interaction between *ADRB2* and socioeconomic deprivation to varying definitions of socioeconomic deprivation. When neighborhood socioeconomic deprivation was defined by median household income less than the median household income for the cohort as a whole, we observed a positive, albeit weaker, interaction among cases (adjusted case-only OR: 1.3, 95% CI: 1.0, 1.6). In this analysis, the evidence that no gene-environment association was present in controls was also weaker (adjusted control-only OR: 1.2, 95% CI: 0.77, 1.8). More generally, a kernel density plot of household income and Gln27Glu status among cases and controls showed a left shift in neighborhood median household income among cases that was not present among controls (Figure). By contrast, a kernel density plot of tract population density by Gln27Glu status in cases (available in eAppendix 1) showed almost difference between high and low-risk variants. Similar kernel density plots of tract family income and tract housing vacancy by Gln27Glu status for both cases and controls are presented in eAppendices 2 and 3. However, the positive case-only interaction did not hold when we dichotomized median family income at the median observed value (adjusted case-only OR: 1.0, 95% CI: 0.82, 1.3, adjusted control-only OR: 1.4, 95% CI: 0.97, 2.1). Analyses of the interaction between Gln27Glu and socioeconomic deprivation in which cases were limited to those aged 79 and younger were comparable to those using all cases (adjusted case-only OR: 2.0, 95% CI: 1.1, 3.5). Finally, an analysis of Gln27Glu variant of the 1443 cases for whom genetic principal component data was available yielded similar results to our original findings for interaction with neighborhood socioeconomic deprivation (case-only OR: 1.9, 95% CI: 1.1, 3.1 adjusting for age and sex but not principal components; case-only OR: 1.8, 95% CI: 1.1, 3.0 adjusting for age, sex, and first 5 identified principal components).

DISCUSSION

This study investigated interactions between neighborhood socioeconomic deprivation- and population density- and the *ADRB2* genotype as associated with sudden cardiac arrest. Our results suggest that, among individuals of European descent, socioeconomic deprivation positively interacts with the high-risk *ADRB2* genotype on the multiplicative scale. Interactions between population density and the *ADRB2* genotype were in the positive direction but less pronounced.

Our findings contribute to the ongoing search for mechanistic links between socioeconomic deprivation and cardiac arrest.[29] Some researchers have suggested that psychosocial stress serves as a key link between deprivation and cardiac arrest,[5] whereas others have suggested deprivation acts upon health through material rather than psychosocial pathways (for example, deprived individuals are less likely to be insured, which may lead to acute hospitalizations that would have been prevented had risk factors been recognized in a routine checkup prior to the acute event). [3] While these hypotheses are not mutually exclusive in practice, they make different predictions about deprivation interacting with *ADRB2*: the materialist hypothesis predicts no interaction, whereas the stress hypothesis does predict interaction. Our finding of an apparent interaction is thus consistent with the stress hypothesis, though our data do not allow us to infer a mechanistic interaction in the sufficient cause sense.[30]

It may be that living in a socioeconomically deprived neighborhood is an indicator of occupational stress rather than or in addition to a source of stress on its own. Previous research suggests occupational stress may be a source of elevated sudden cardiac arrest risk.[31] Workers in less skilled, lower socioeconomic status jobs, who might more often live in lower socioeconomic status neighborhoods, reported higher levels of occupational stress.[32,33] If the stress pathway proves to be the cause of associations between socioeconomic status and sudden cardiac arrest risk, further work distinguishing the effects of occupational stress from the effects of residential neighborhood stress will be needed.

Our primary interaction analysis focused on a single missense variant in *ADRB2*, Gln27Glu, which has previously been associated with elevated sudden cardiac arrest risk in this and other populations.[14,15] Because Gln27Glu is in linkage disequilibrium with another *ADRB2* missense variant, Arg16Gly, we also analyzed Arg16Gly/Gln27Glu diplotypes. In this analysis, results suggested elevated risk in those missing an H1 haplotype, consistent with Gln27Glu rather than Arg16Gly being the relevant mutation. However, estimates in the diplotype analysis were imprecise, and replication of this finding in larger datasets is necessary before any conclusions can be drawn.

If the stress pathway is the link between socioeconomic status and sudden cardiac arrest, it may be of interest to examine environmental interactions with additional genes with known links to sudden cardiac arrest to more fully investigate the specificity of the interaction. For example, the angiotensin-converting enzyme (ACE) gene is involved in neural pathways similar to *ADRB2*'s function in the sympathetic nervous system and has previously been linked to sudden cardiac arrest.[22] Variations in angiotensin receptor type I (AGTR1) and type 2 (AGTR2) have also been linked to cardiovascular outcomes within other studies.[34,35]

Similarly, if exposure to stressors is necessary for Gln27Glu substitution to result in elevated sudden cardiac arrest risk, this may help to explain inconsistencies in risk associated with ADRB2 variant observed in prior studies. Specifically, several prior study populations in which no associations or weak associations between ADRB2 and sudden cardiac arrest were identified were recruited from populations that were already in clinical care[17] or were healthcare professionals.[15] By contrast, the Cardiovascular Health Study, where a strong positive association was observed, was a population-based sample.[14] We note, however, that

these prior studies included other population differences, including prevalence of known coronary artery disease, and measurement differences, including sudden cardiac arrest identification, that may also explain the inconsistent findings.[17]

Our interaction analysis also focused on two neighborhood characteristics, population density and socioeconomic deprivation, presumed to be associated with elevated exposure to neighborhood stressors. However, other environmental exposures, such as particulate matter air pollution, may increase sudden cardiac arrest risk.[36] Socioeconomically deprived neighborhoods often endure greater exposure to air pollution than less deprived neighborhoods.[37] It is therefore possible that our operationalization of high-stress neighborhoods acts as a proxy for high-pollution neighborhoods, and that the interaction with *ADRB2* gene is in response to air pollution rather than psychosocial stress. While there is less biological evidence predicting an interaction between air pollution and *ADRB2*, this hypothesis may nonetheless benefit from future research.

Our finding was robust to a sensitivity analysis that defined neighborhood deprivation by dichotomizing median household income, but not to one that defined neighborhood deprivation by dichotomizing median family income. Measures of family income are computed from households in which two or more residents are related by blood or marriage, whereas measures of household income include all residents.[38] Further investigation of how neighborhood conditions operate as a stressful exposure, including any role of household composition, may be warranted.

Our conclusions are strengthened by the relatively large number of sudden cardiac arrest cases, population-based control sampling strategy, and conservative case definition used in this analysis. The robustness of our primary result to an analysis controlling for genetic principal components was also reassuring.

However, our results should be considered in light of several limitations. First, while our environmental exposures of interest were neighborhood characteristics, because most residents of crowded and socioeconomically deprived neighborhoods are themselves socioeconomically deprived, it is possible that these neighborhood characteristics act as proxies for individual socioeconomic status or other correlated exposures, such as tobacco use. Our study is thus testing a hypothesis of effect heterogeneity of *ADRB2* variant by neighborhood rather than a causal interaction of *ADRB2* and neighborhood.[39] While effect heterogeneity of *ADRB2* across levels of socioeconomic deprivation would still be consistent with the stress hypothesis described above, future research distinguishing risk attributable to correlated behaviors from risk attributable to neighborhood stressors would be valuable. Second, owing to limitations of the data available for analysis, our study was restricted to individuals of European descent living in the northwestern United States; few of whom lived in socioeconomically deprived neighborhoods. Prior research indicates that substantial differences exist between ethnicities in exposure to stressors and in stress coping mechanisms;[40] it is therefore important to investigate the relationship observed here in other ethnic groups and other socioeconomic contexts. Third, we excluded about a quarter of subjects owing to geocoding difficulties, raising the possibility of selection bias if the distribution of genetic variants or neighborhood conditions was different for excluded

subjects. Fourth, though our analysis of population-based controls revealed no evidence of a gene–environment association that would render the case-only analysis invalid, we do not have data from a control population recruited under the same criteria as the cases. Because the control population is small and the neighborhood exposure was rare, we are unable to rule out the possibility that a gene-environment association exists among King County residents at risk for sudden cardiac arrest. Such an association would call into question the validity of our results. However, if the true association were in the negative direction suggested by our observed data, the case-only design would underestimate the true association.[27] Finally, our case-only odds ratio estimates were imprecise and our findings are compatible with a wide range of effect sizes, including some that were very small.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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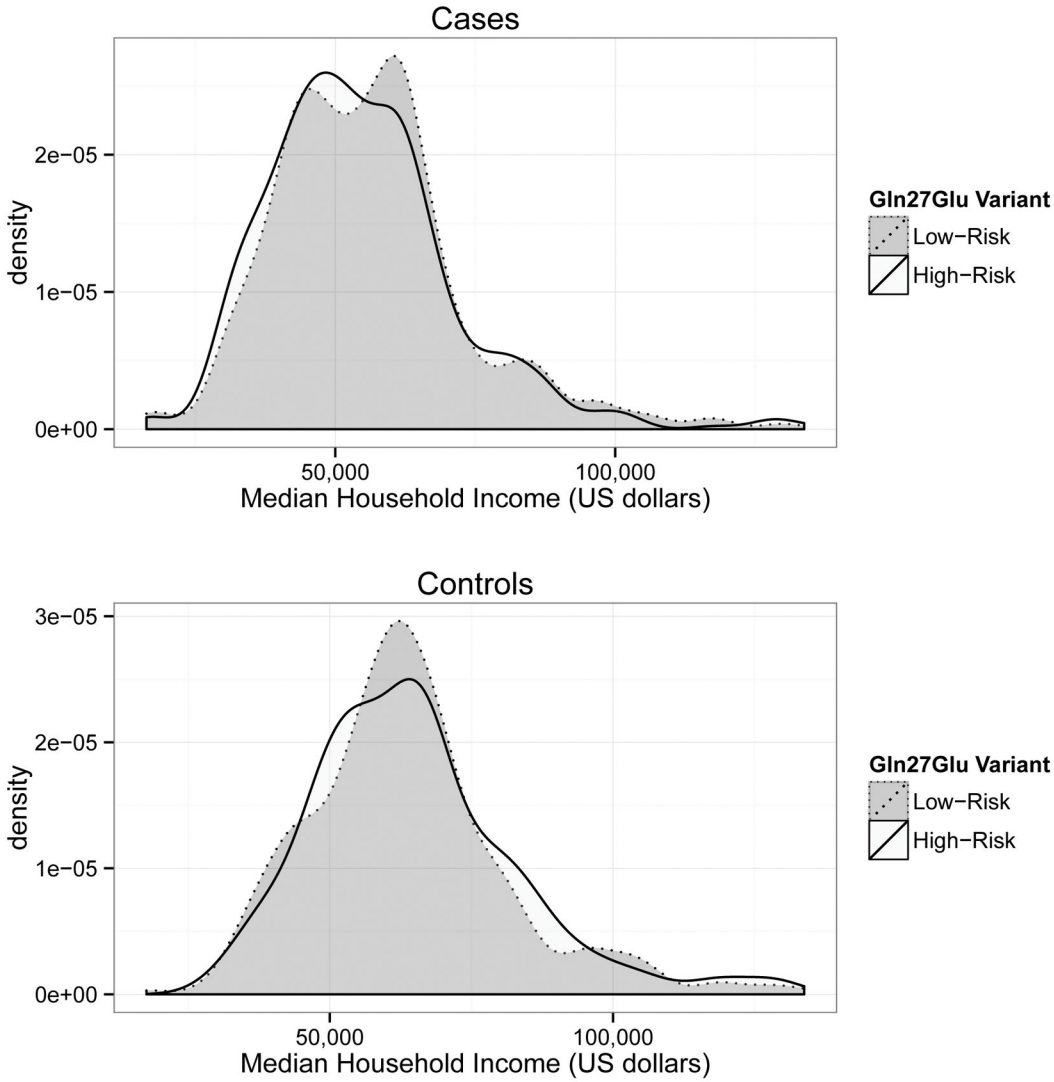

FIGURE.

Kernel density plots of median household income as associated with *ADRB2* genotype in 1,539 sudden cardiac arrest cases and 480 controls recruited from King County, Washington between 1988 and 2004. The high-risk Gln27Glu variant (homozygous Gln27) is associated with a left-shifted curve (i.e. living in neighborhoods with less socioeconomic resources) in cases but not in controls. This is consistent with the hypothesized gene-environment interaction between *ADRB2* and neighborhood socioeconomic conditions in causing sudden cardiac arrest.

TABLE 1

Descriptive characteristics of subjects and 2000 US Census characteristics of their home census tract, King County, WA (Seattle), 1988–2004.

	Cardiac Arrest Cases (n = 1,539)		Population-Based Controls (n = 480)	
	Median (IQR)	%	Median (IQR)	%
Age, years	71 (61, 79)		58 (50, 66)	
Male		75		78
Tract income, US $	67,212 (54,690, 79,330)		72,045 (62,400, 82,950)	
Population density, residents/km^2	2,273 (1,566, 3,131)		1,496 (972, 2,249)	
Average floor space per home, m^2	151 (135, 182)		173 (150, 203)	
High-Risk[a] Gln27Glu SNP		31		30
ADRB2 Diplotypes[b]				
H1H1		20		19
H1H2		32		35
H1H3		17		16
H2H2		13		13
H2H3		14		15
H3H3		4		2

[a]Homozygous for Gln27.

[b]H1 indicates Gly16Glu27; H2 indicates Arg16Gln27; H3 indicates Gly16Gln27.

IQR indicates interquartile range; SNP, single nucleotide polymorphism

TABLE 2

Relation of *Gln27Glu* genotype and neighborhood characteristics stratified by case status, King County, WA (Seattle), 1988–2004.

		Socioeconomically Deprived[a]			High Population Density[b]		
		Exposed	Unexposed	Odds Ratio[c] (95% CI)	Exposed	Unexposed	Odds Ratio[c] (95% CI)
Cases	**High-Risk**[d]	28	451	1.8 (1.0, 2.9)	283	196	1.2 (0.97, 1.5)
	Low-Risk	36	1,024		581	479	
Controls	**High-Risk**[d]	1	141	0.35 (0.018, 2.0)	36	106	0.82 (0.52, 1.3)
	Low-Risk	7	331		99	239	

CI indicates confidence interval.

[a] Neighborhoods with median family income ≤ 80% of the King County median family income were considered socioeconomically deprived

[b] Neighborhoods above the median population density among cases and controls were considered high population density.

[c] Adjusted for age and sex.

[d] High-risk was defined as homozygous for Gln27.

TABLE 3

Relation of *ADRB2* diplotype and neighborhood characteristics in cases, King County, WA (Seattle), 1988–2004.

	Socioeconomically Deprived[a]			High Population Density[b]		
Diplotype[c]	**Exposed**	**Unexposed**	**Odds Ratio[d] (95% CI)**	**Exposed**	**Unexposed**	**Odds Ratio[d] (95% CI)**
H1H2	17	462	REF	216	263	REF
H1H1	10	287	0.94 (0.41, 2.0)	134	163	1.0 (0.76, 1.4)
H1H3	9	249	0.99 (0.41, 2.2)	118	140	0.97 (0.71, 1.3)
H2H2	11	190	1.6 (0.70, 3.5)	84	117	1.2 (0.82, 1.6)
H2H3	13	196	1.8 (0.83, 3.7)	91	118	1.1 (0.79, 1.5)
H3H3	3	55	1.4 (0.33, 4.4)	22	36	1.4 (0.79, 2.4)

CI indicates confidence interval.

[a] Neighborhoods with median family income ≤ 80% of the King County median family income were considered socioeconomically deprived

[b] Neighborhoods above the median population density among cases and controls were considered high population density.

[c] H1 indicates Gly16Glu27; H2 indicates Arg16Gln27; H3 indicates Gly16Gln27

[d] Adjusted for age and sex.