A Polymorphism in the β1 Adrenergic Receptor Is Associated with Resting Heart Rate

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Resting heart rate is significantly associated with cardiovascular morbidity and mortality. However, the extent to which resting heart rate is genetically determined is poorly understood, and no genes have been found that contribute to variation in resting heart rate. Because signaling through the β1 adrenergic receptor is a key determinant of cardiac function, we tested whether polymorphisms in this receptor are associated with resting heart rate. A cohort of >1,000 individuals of Chinese and Japanese descent, from nuclear families, was genotyped for two polymorphisms, resulting in a serine/glycine substitution at amino acid 49 (Ser49Gly) and an arginine/glycine substitution at residue 389 (Arg389Gly), in the β1 adrenergic receptor. For comparison, polymorphisms in the β2 and β3 adrenergic receptors were also evaluated. The Ser49Gly polymorphism was significantly associated ($P = .0004$) with resting heart rate, independent of other variables, such as body-mass index, age, sex, ethnicity, exercise, smoking, alcohol intake, hypertension status, and treatment with beta blockers. The data support an additive model in which individuals heterozygous for the Ser49Gly polymorphism had mean heart rates intermediate to those of either type of homozygote, with Ser homozygotes having the highest mean heart rate and with Gly homozygotes having the lowest. Neither the Arg389Gly polymorphism in the β1 adrenergic receptor nor polymorphisms in the β2 and β3 adrenergic receptors were associated with resting heart rate. The heritability of heart rate was 39.7% ± 7.1% ($P < 10^{-7}$).

Introduction

Resting heart rate is significantly correlated with cardiovascular morbidity and mortality (Dyer et al. 1980; Kannel et al. 1987; Gillman et al. 1993; Greenland et al. 1999; Kristal-Boneh et al. 2000). For example, in the Framingham study, in a sample of >5,000 subjects who did not have cardiovascular disease at the time of entry into study, cardiovascular and coronary mortality increased progressively with resting heart rate, thus supporting a causal relationship between heart rate and subsequent development of heart disease (Kannel et al. 1987). More recently, another follow-up study, comprising >3,000 Israeli men who were free of cardiovascular disease at the time of entry into study, indicated that resting heart rate was significantly associated with cardiovascular mortality after other risk factors had been controlled for (Kristal-Boneh et al. 2000).

These observations suggest that knowing the genetic determinants of heart rate might provide clues to the etiology of heart disease and even permit the identification of individuals at elevated risk of development of heart disease. Recent studies indicate that, at least in some white populations, genes explain a significant proportion of the variation seen in resting heart rate (Ditto 1993; Singh et al. 1999); however, the general applicability of these estimates of heritability is not known. Furthermore, specific genes that make a significant contribution to heart rate are also not known. In contrast, numerous studies have revealed other factors—such as cigarette smoking, regular physical activity, stress, hypertension, and treatment with beta blockers—that influence heart rate (Blackburn et al. 1960; Thomas 1960; Higgins and Kjelsberg 1967; Goldbourt and Medalie 1977; Manuck and Garland 1980; Gillum 1988; The Beta-Blocker Evaluation of Survival Trial Investigators 2001).

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Cardiac function is regulated by a variety of mechanisms. However, it appears that epinephrine and norepinephrine, acting through specific β-adrenergic receptors, play a critical role in regulating both the frequency and the force of contraction of the heart (Insel 1996). On the basis of their ability to distinguish different ligands, beta-adrenergic receptors can be divided into three types. The β1 adrenergic receptor is the predominant subtype expressed in the heart, and a number of studies have made it clear that signaling through this receptor subtype is important for both cardiac chronotropy and cardiac inotropy (Rohrer et al. 1996, 1999; Engelhardt et al. 1999). Moreover, signaling through the β1 adrenergic receptor is decreased in the failing heart (Bristow et al. 1986, 1993). The β2 adrenergic receptor is thought to regulate vascular smooth-muscle relaxation, and the β3 adrenergic receptor has been implicated in the control of lipolysis in adipose tissue.

For these reasons, we hypothesized that polymorphisms in the β1 adrenergic receptor might contribute to variation in resting heart rate. The large sample of middle-aged individuals of Chinese and Japanese origins whom we have collected in an effort to identify genes for essential hypertension and related phenotypes have provided an opportunity to test this hypothesis. Here we show that a single-nucleotide polymorphism (SNP) that results in a serine/glycine amino acid substitution in the β1 adrenergic receptor is associated with resting heart rate in this population.

Subjects and Methods

Subjects

Individuals were recruited as part of the Stanford, Asia, Pacific Program for Hypertension and Insulin Resistance (SAPPHIRe), and details of this study population have been published elsewhere (Ranade et al. 2000). In brief, hypertensive subjects of Chinese and Japanese origins were recruited in the San Francisco Bay Area, Hawaii, and Taiwan. Hypertension was defined as including blood pressure (BP) in the upper 20% of the BP distribution of untreated individuals. In our study population, this threshold translated into the following values: (*a*) systolic BP (SBP) $\geq$160 mmHg and/or diastolic BP (DBP) $\geq$95 mmHg or (*b*) treatment with two medications for high blood pressure (stage II hypertension). Alternatively, the subject had uncontrolled hypertension—that is, was taking one medication for high blood pressure and had either systolic BP $\geq$140 or diastolic $\geq$90 mmHg. Comparably hypertensive siblings of the proband, as well as low-normotensive sibs were also recruited. "Low-normal" BP was defined as BP in the bottom 30% of the age- and sex-adjusted BP distribution, which, in our study population, translated into the following BP values: for men <45 years of age, low-normal BP was defined as systolic BP $\leq$115 mmHg and diastolic BP $\leq$76; for men >45 years of age, systolic BP $\leq$122 and diastolic $\leq$78; for women <45 years of age, systolic BP $\leq$107 and diastolic BP $\leq$70 mmHg; and, for women >45 years of age, systolic BP $\leq$118 and diastolic BP $\leq$75. Individuals with chronic illnesses such as diabetes or heart, liver, or kidney diseases or cancer were excluded from the study; however, individuals in whom diabetes had been diagnosed as a result of tests performed by us were not excluded.

Resting heart rate and resting blood pressure were determined simultaneously, by use of an oscillometric device, the Dinamap model 1846 SX (Critikon). The subject was seated with legs uncrossed and was asked to refrain from talking for 5 min. Blood-pressure and heart-rate measurements were taken three times, with at least a 1-min time lapse between two consecutive readings, and the average of the second and third readings was used in the analysis. To ensure uniform measurements at the different sites, technicians/clinicians at all the sites were trained to measure BP by use of this protocol, and they were monitored annually during site visits. Furthermore, there was a centralized retraining and recertification of key technicians each year.

In this study, 1,348 individuals were evaluated. The distribution of family sizes was as follows: 199 singletons and 252, 120, 41, 17, and 6 families with two, three, four, five, and six sibs, respectively.

This study was approved by institutional review boards at all participating sites, and informed consent was obtained from all subjects.

Genotyping

Genotyping was performed by the TaqMan assay, as described elsewhere (Ranade et al. 2001). Subjects were typed for two polymorphisms that result in serine/glycine (Ser49Gly) and arginine/glycine (Arg389Gly) amino acid substitutions at residues 49 and 389, respectively (Maqbool et al. 1999; Mason et al. 1999). Three polymorphisms in the β2 adrenergic receptor were evaluated. One is a C/T transition (C-47T) in the leader cistron (McGraw et al. 1998). The other two result in glycine/arginine (Gly16Arg) and glutamate/glutamine (Glu27Gln) amino acid substitutions at residues 16 and 27, respectively (Reihsaus et al. 1993). A polymorphism in the β3 adrenergic receptor, which results in a tryptophan/arginine (Trp64Arg) amino acid substitution at residue 64 (Walston et al. 1995), was also examined. The probes and primers used in the TaqMan assay were as follows (in each probe, the polymorphic nucleotide is underlined). For the SNPs in the β1 adrenergic–receptor gene, the probes and primers were as follows: for Ser49Gly, the probes were CCAGCGAAAGCCCCGAGCC and CCAGCGAAGGCCCCGAGC, and the primers were GTCGCCGCCCGCCTCGTT and CCATGCCCGCTGTCCA-

CTGCT; and, for Arg389Gly, the probes were AGGCCTTCCAGCGACTGCTCTGC and AGGCCTTCCAGGGACTGCTCTGCT and the primers were GGCCTTCAACCCCATCATCTA and CCGGTCTCCGTGGGTCGCGT. For SNPs in the β2 adrenergic–receptor gene, the probes and primers were as follows: for C-47T, the probes were CGCCTCAGCGGGCGGACCC and CGCCTCAGCAGGCGGACCC, and the primers were GCTGAATGAGGCTTCCAGGCGT and GCGCGCAGTCTGGCAGGTAA; for Gly16Arg, the probes were CGCATGGCTTCCATTGGGTGC and CGCATGGCTTCTATTGGGTGC, and the primers were GGAACGGCAGCGCCTTCT and CAGGACGATGAGAGACATGACGAT; and, for Glu27Gln, the probes were CTCGTCCCTTTCCTGCGTGACGT and CTCGTCCCTTTGCTGCGTGACGT (the primers used in this assay were the same as those used for Gly16Arg). For the Trp64Arg SNP in the β3 adrenergic receptor, the probes were TCTCGGAGTCCAGGCGATGGCCA and CTCGGAGTCCGGGCGATGGCC, and the primers were GGAGGCAACCTGCTGGTCAT and CACGAACACGTTGGTCATGGT.

Statistical Analysis

Heart rates were natural-log transformed to approximate normality and then were used in the statistical analysis. In a preliminary analysis, the effect that the β adrenergic receptor has on resting heart rate was examined by one-way analysis of variance. Significant results were then followed up by multivariate analysis, as described below. Heritability of resting heart rate was estimated by the program SOLAR, with the entire sibship being considered in the analysis, under the assumption of a multivariate normal distribution (Almasy and Blangero 1998). The influence that the β1 adrenergic–receptor genotype and other covariates have on resting heart rate was estimated simultaneously in a multivariate analysis, also by the program SOLAR. In addition to the β1 adrenergic–receptor genotype, this analysis included, as covariates, BMI, age, sex, ethnicity, hypertension status, antihypertensive medications (beta blockers, ACE inhibitors, calcium-channel blockers, and diuretics), smoking, alcohol intake, and exercise. SOLAR estimates what proportion of variance is explained, in the presence of background polygenic variance, by a covariate, thus allowing for familial correlation in heart rate. The program also takes into account the nonindependence of sib genotypes. Smoking and alcohol use were evaluated as continuous variables, as number of cigarettes per day and number of drinks per month, respectively. We derived a measure of physical activity, essentially as described by Ainsworth et al. (2000), and used this metric in the analysis.

For estimation of linkage disequilibrium between SNPs, one individual was chosen at random from each of the families studied, and pairwise haplotype frequencies were estimated on the basis of data from these 635 individuals, by the expectation-maximization algorithm as implemented in the EH program (see the Web site of the Lab of Statistical Genetics at Rockefeller University). Linkage-disequilibrium values (D') were calculated as described elsewhere (Lewontin 1964).

Results

We evaluated 1,348 subjects in this study (for details of the study population, see table 1). On the basis of correlations within entire sibships, we estimate the heritability of heart rate at 39.7% ± 7.1% ($P < 10^{-7}$) in our study population, an estimate similar to that derived in the Framingham study (~46%) (Singh et al. 1999).

We typed subjects for two polymorphisms in the β1 adrenergic–receptor gene; the first polymorphism resulted in a serine/glycine amino acid substitution at position 49 (Ser49Gly), and the second resulted in an arginine/glycine substitution at position 389 (Arg389Gly). We evaluated the influence that these polymorphisms had on heart rate, in a multivariate analysis that included, as covariates, BMI, age, ethnicity, sex, cigarette smoking, alcohol intake, exercise, antihypertensive-medication use, and hypertension status.

The Ser49Gly polymorphism was significantly associated ($P = .0004$) with resting heart rate (table 2). Individuals homozygous for the Ser allele had the highest mean heart rate (69.4 beats per minute [bpm]), heterozygotes had an intermediate heart rate (67.7 bpm), and Gly homozygotes had the lowest heart rate (64.2 bpm). These observations suggest an additive model, with every Ser allele increasing heart rate. The polymorphism appeared to have a significant impact on heart rate, because the difference, in mean values, between the two classes of homozygotes was almost half a standard deviation. The Arg389Gly variant, in contrast, was not associated ($P > .05$) with resting heart rate. Consistent with these results, there was only weak linkage disequilibrium be-

Table 1

Study Population

Characteristic	Chinese	Japanese
Sex (M/F)	493/529	137/189
Affection status:		
Low normotensive	321	38
Hypertensive	701	288
Medication status[a]	612	260
Mean age ± SD (years)[b]	49.8 ± 8.3	55.2 ± 8.1
Mean BMI ± SD (kg/m^2)[b]	25.4 ± 3.4	26.5 ± 3.7

[a] Number of patients with hypertension who are taking antihypertensive medication.

[b] The mean for the low-normotensive group was 47.3 ± 7.6 years; that for the hypertensive group was 52.3 ± 8.3 years.

Table 2

Mean Heart Rate, by β Adrenergic–Receptor Genotype

Adrenergic-Receptor Gene and SNP	Mean Heart Rate ± SD(*N*)[a] (bpm)			*P*[b]
	Genotype 1/1	Genotype 1/2	Genotype 2/2	
β1:				
Ser49Gly	69.4 ± 11.0 (996)	67.7 ± 10.8 (317)	64.2 ± 9.8 (35)	.0004
Arg389Gly	68.7 ± 11.14 (782)	68.6 ± 10.6 (489)	72.0 ± 11.8 (77)	.68
β2:				
C-47T	67.6 ± 8.7 (12)	66.4 ± 11.2 (149)	68.8 ± 11.1 (850)	.06
Gly16Arg	68.8 ± 11.1 (292)	68.3 ± 10.9 (665)	69.7 ± 11.0 (374)	.17
Glu27Gln	68.2 ± 8.3 (15)	68.3 ± 10.8 (185)	69.0 ± 11.1 (1,145)	.74
β3:				
Trp64Arg	68.8 ± 10.9 (942)	69.2 ± 11.3 (368)	67.0 ± 8.7 (26)	.57

[a] All statistical inferences are based on log-transformed heart rates, but, for clarity, heart rates in the untransformed scale are given.

[b] Values for β1 adrenergic receptor SNPs are obtained from a multivariate analysis; for the other SNPs, values are from one-way analysis of variance (see the "Statistical Analysis" section and table 3). For each SNP, 1/1 denotes homozygosity for the first amino acid or base pair listed in the leftmost column, 1/2 denotes heterozygosity, and 2/2 homozygosity for the second amino acid or base pair listed in the leftmost column; thus, for the Ser49Gly SNP, 1/1 = Ser/Ser, 1/2 = Ser/Gly, and 2/2 = Gly/Gly.

tween the Ser49Gly and Arg389Gly variants ($D' = 0.29$; $\chi^2_{1\,df} = 39.18$) in our study population.

For comparison, we also examined, for association with resting heart rate, polymorphisms in the β2 and β3 adrenergic receptors (table 2). These analyses included glycine/arginine (Gly16Arg) and glutamate/glutamine (Glu27Gln) polymorphisms at residues 16 and 27, respectively, in the β2 adrenergic receptor and a third polymorphism (C-47T) in the leader cistron of this gene. For the β3 adrenergic–receptor gene, we evaluated a tryptophan/arginine (Trp64Arg) polymorphism at residue 64. As expected, there was no evidence of association between these polymorphisms and resting heart rate.

As shown in table 3, age, ethnicity, and hypertension status were strongly predictive ($P < .0001$) of resting heart rate; sex was less significantly associated ($P = .001$). BMI, smoking, alcohol intake, and exercise were not significantly associated with heart rate, however. As expected, use of beta blockers was highly significantly associated with heart rate. Hypertensive subjects receiving beta-blocker therapy had a lower mean heart rate (65.3 bpm) than did those receiving other types of antihypertensive medication (69.8 bpm) ($P < 10^{-7}$). Use of other antihypertensive medicines that were frequently prescribed (i.e., calcium-channel blockers, ACE inhibitors, and diuretics) was not associated with heart rate, however.

We stratified the population on the basis of ethnicity, the site where subjects were recruited, and medication status, and we examined mean heart rates by genotype (table 4). In general, subjects with the Ser/Gly or Gly/Gly polymorphism had consistently lower mean heart rates than did Ser/Ser homozygotes, regardless of eth-

Table 3

Influence of Covariates, Including Ser49Gly Genotype, on Heart Rate in a Multivariate Model

Covariate	*P*
β1 Adrenergic–receptor genotype:	
Ser49Gly	.0004
Arg389Gly	.68
Demographic variables:	
Age	.00004
Ethnicity	.00002
Sex	.001
Hypertension status	.000005
Hypertensive medications:	
Beta blockers	<.0000001
ACE inhibitors	.17
Calcium-channel blockers	.10
Diuretics	.13
Other:	
BMI	.08
Cigarettes/day	.18
Alcohol/month	.96
Exercise	.89

Note.—Heart rate and the other covariates noted above were analyzed simultaneously in a multivariate model using SOLAR. The regression coefficients and their SEs, for age, sex, ethnicity, hypertension status, and beta-blocker use, were −0.127 (0.037), 0.814 (0.570), −2.758 (0.782), 3.054 (0.725), and −5.068 (0.608), respectively. The categorical variables were coded as follows: sex—male = 0, female = 1; ethnicity—Chinese = 0, Japanese = 1; hypertension status—unaffected = 0, affected = 1; and beta-blocker use—untreated = 0, treated = 1.

nicity, geographic origin, or medication status. The exceptions were the small number of unmedicated hypertensive individuals (UH [$N = 117$]) and the group recruited at National Taiwan University (NTU [$N = 183$]). This apparent inconsistency is almost certainly due to the small sample size of each group. When the cohort from Taiwan was examined as a whole, mean heart rates for the three different genotypes were entirely consistent with those seen at the other sites. Furthermore, the difference, in mean heart rates, between Ser49 homozygotes and heterozygotes in both strata, compared to that in the complementary strata, is not statistically significant (K.R. and N.R., unpublished observations). Thus, there is no evidence of heterogeneity among any of the defined strata. We also examined sibships that had at least one Ser/Gly heterozygote and one of the other genotypes—that is, families that were segregating the minor Gly49 allele. As in the overall sample, Ser/Gly heterozygotes and Gly/Gly homozygotes had lower mean heart rates than did Ser/Ser homozygotes. Taken together, these results suggest that the association between the Ser49Gly SNP and heart rate is unlikely to be confounded by either population stratification or antihypertensive medication (specifically, treatment with beta blockers). It is noteworthy that the magnitude of the effect that the Ser49Gly genotype had on heart rate was the same in both the low-normotensive group comprising >350 individuals and in the hypertensive group (see table 4). In both groups, the difference, in heart rates, between Gly/Gly homozygotes and Ser/Ser homozygotes was approximately half a standard deviation.

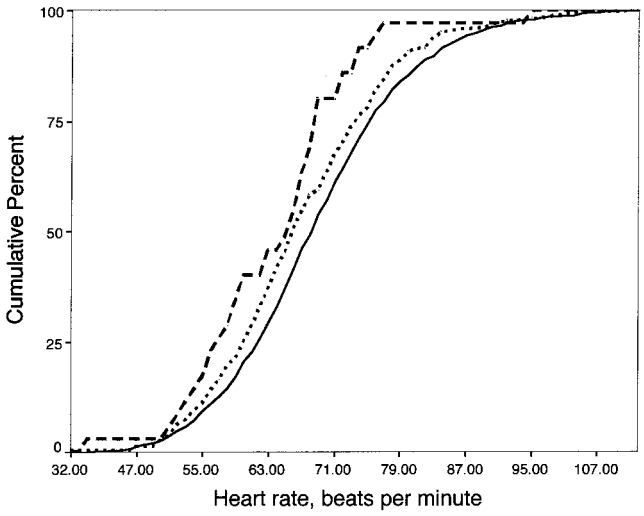

Figure 1 Cumulative distributions of heart rate, by Ser49Gly genotype. The solid line indicates results for Ser49 homozygotes, the dotted line indicates results for Ser/Gly heterozygotes, and the dashed line indicates results for Gly49 homozygotes. The percentage of individuals with heart rates lower than a certain value can be read off the *Y*-axis.

We next compared the distributions of heart rates for the three Ser49Gly genotypes (fig. 1). It appeared that the entire distributions of the Ser/Gly and Gly/Gly gen-

Table 4

β1 Adrenergic–Receptor Genotypes and Heart Rates, Stratified by Ethnicity, Geographical Origin, and Medication Status and within Sibships

Stratum	Mean Heart Rate ± SD, for Ser49Gly Genotype (*N*) (beats/min)		
	Ser/Ser	Ser/Gly	Gly/Gly[a]
Ethnicity:			
Chinese	70.3 ± 11.1 (749)	68.2 ± 10.7 (251)	65.2 ± 6.6 (22)
Japanese	66.7 ± 10.4 (247)	65.6 ± 11.1 (66)	62.4 ± 13.8 (13)
Site:			
San Francisco Bay	63.4 ± 8.6 (95)	62.4 ± 8.1 (36)	58.0 ± 9.5 (3)
Hawaii	66.9 ± 10.5 (258)	66.1 ± 11.8 (79)	63.7 ± 15.0 (10)
Taiwan:			
Tri-Services General Hospital, Taipei	70.7 ± 10.6 (161)	66.7 ± 8.5 (47)	67.3 ± 7.0 (10)
National Taiwan University, Taipei	70.4 ± 11.2 (145)	72.0 ± 12.0 (38)	NA
Veterans General Hospital, Taipei/Taichung	72.0 ± 11.2 (337)	69.3 ± 10.5 (117)	63.5 ± 6.0 (12)
Overall	71.3 ± 11.1 (643)	69.2 ± 10.5 (202)	65.2 ± 6.6 (22)
Medication:			
Unmedicated:			
Low normotensive	70.1 ± 9.3 (277)	68.4 ± 9.3 (75)	66.3 ± 5.6 (7)
Hypertensive	74.4 ± 12.0 (93)	74.0 ± 15.3 (23)	76.0 (1)
Hypertensive subjects taking antihypertensive medication	68.3 ± 11.4 (626)	66.7 ± 10.5 (219)	63.2 ± 10.5 (27)
Sibships:			
Families with Ser/Gly subjects	68.8 ± 9.5 (165)	67.7 ± 11.2 (165)	64.7 ± 5.7 (16)

[a] NA = not applicable (there were no Gly/Gly homozygotes at this site).

otypes were shifted toward lower heart rates, although the effect was most apparent for the Gly/Gly genotype.

A very recent study from Sweden has suggested that homozygosity for the Arg allele of the Arg389Gly polymorphism of the β1 adrenergic receptor is associated with hypertension (Bengtsson et al. 2001). In our study population, however, the Arg allele was not associated with either increased blood pressure or hypertension status (table 5). In contrast, homozygosity for the Gly allele of the Ser49Gly polymorphism was associated with modestly decreased blood pressures. This observation is consistent with the lower heart rates of Gly49 homozygotes. This decrease in blood pressure, however, was not statistically significant.

Discussion

We have evaluated two polymorphisms in the β1 adrenergic receptor—which result in serine/glycine and arginine/glycine amino acid substitutions at positions 49 and 389, respectively—for association with resting heart rate. The Ser49Gly variant was significantly associated ($P = .0004$) with heart rate, independent of other variables—such as age, sex, ethnicity, hypertension status, and beta-blocker use—that also had a significant influence on heart rate. Remarkably, the effect that the Ser49Gly genotype had on heart rate was similar to that of beta-blocker therapy—that is, homozygosity for the Gly49 allele and beta-blocker use both decreased heart rate by ~5 bpm. In contrast, the Arg389Gly variant was not significantly associated with heart rate. However, we note that Gly389 homozygotes had a higher mean heart rate than did the subjects with either of the other two genotypes (table 2). If, as these data suggest, the Gly389 allele is recessive, then the lack of a significant effect might be due to the small number of Gly389 homozygotes in our study.

In contrast to the association between Ser49Gly genotype and resting heart rate, there was no evidence of association between polymorphisms in the β2 and β3 adrenergic receptors and heart rate. These results underscore the importance that signaling through the β1 adrenergic receptor has for cardiac function, and they further highlight the difference among these β adrenergic–receptor subtypes.

The association between Ser49Gly genotype and resting heart rate is robust to population stratification, because the Gly49 allele consistently decreased heart rate—regardless of ethnicity or site of recruitment and, perhaps most importantly, even within sibships that were segregating the Gly49 allele (table 4). The association also is robust to confounding by the use of beta blockers, for two reasons. First, Ser49Gly genotype was significantly associated with resting heart rate even when beta-blocker use was a covariate in the analysis, indicating that Ser49Gly genotype is associated with heart rate, independent of treatment with beta blockers (table 3). Second, the magnitude of the effect that the Ser49Gly genotype has on heart rate was similar (approximately half a standard deviation) in the large number of low-normotensive subjects ($N = 359$) who were not treated with beta blockers and in the hypertensive group taking beta blockers (table 4). The similar effect that this SNP has on heart rate in both the low-normotensive and hypertensive groups, together with the fact that our study population is middle-aged (average age 47.3 and 52.3 years for the low-normotensive and hypertensive groups, respectively), suggests that the association between Ser49Gly and heart rate might be generalizable to the population at large.

The Gly49 residue is evolutionarily highly conserved from rat through human (Podlowski et al. 2000), suggesting that replacing this residue with serine could affect the function of the β1 adrenergic receptor. Since this amino acid residue is in the extracellular portion of the receptor—and is not in proximity to the hormone-binding site—an appealing hypothesis is that this residue is important for receptor trafficking, perhaps af-

Table 5

β1 Adrenergic–Receptor Genotypes and Blood Pressure

SNP and Genotype	Mean Blood Pressure ± SD(*N*) (mmHg)			
	Low Normotensive		Hypertensive[a]	
	Systolic	Diastolic	Systolic	Diastolic
Ser49Gly:				
Ser/Ser	104.8 ± 8.1 (277)	65.0 ± 6.5 (277)	141.2 ± 22.9 (719)	82.7 ± 12.9 (719)
Ser/Gly	103.6 ± 10.7 (75)	64.1 ± 7.8 (75)	141.6 ± 19.7 (242)	83.1 ± 11.2 (242)
Gly/Gly	99.3 ± 6.3 (7)	62.6 ± 5.2 (7)	132.8 ± 20.0 (28)	78.4 ± 11.0 (28)
Arg389Gly:				
Arg/Arg	104.1 ± 9.3 (198)	64.5 ± 6.9 (198)	140.6 ± 21.5 (584)	82.4 ± 12.1 (584)
Arg/Gly	104.6 ± 8.1 (138)	64.8 ± 6.5 (138)	141.9 ± 23.2 (351)	82.8 ± 13.2 (351)
Gly/Gly	106.7 ± 6.5 (23)	66.1 ± 7.0 (23)	140.8 ± 21.9 (54)	84.4 ± 11.7 (23)

[a] Blood-pressure readings of these individuals are distorted by antihypertensive medications.

fecting the number of functional molecules on the surface of the cell. This mechanism would be consistent with the dosage effect that the polymorphism has on heart rate. It is possible, however, that the Ser49Gly variant is in tight linkage disequilibrium with another SNP that is, in fact, functionally associated with heart rate. Further studies—of nucleotide variation in the β1 adrenergic–receptor gene and of the impact that the Ser49Gly variant has on the function of the receptor—will be needed to resolve this issue.

On the basis of the strong association between elevated resting heart rate and cardiovascular mortality and our observations that Ser49 homozygotes had higher heart rates, we might expect these individuals to be more susceptible to cardiovascular mortality and Gly49 carriers to be protected from it. We could not address this question, because subjects with overt heart disease were intentionally excluded from our study. However, while this work was in progress, another study reported an association between the Ser49Gly variant and survival times in patients with heart failure. Consistent with our expectation, subjects with a Gly49 allele had better survival rates than did Ser49 homozygotes (Borjesson et al. 2000). A second study suggested that the Gly49 allele was associated with idiopathic dilated cardiomyopathy; however, this finding was based on the study of only 37 patients (Podlowski et al. 2000). In contrast—and consistent with our results showing that the Arg389Gly variant has no effect on heart rate—another case-control study found no evidence of association between this polymorphism and dilated cardiomyopathy (Tesson et al. 1999). Larger studies with sufficient numbers of Gly49 and Gly389 homozygotes will be needed to adequately address this issue.

It is interesting to note that beta blockers decreased heart rate by ~5 bpm, regardless of the Ser49Gly genotype. In contrast, subjects homozygous for the Gly389 allele had a smaller reduction (1.5 bpm) in heart rate than did either Arg389 homozygotes or heterozygotes (5 bpm). This difference was not statistically significant, perhaps because of the small number of Gly389 subjects. However, this observation, as well as the fact that the Arg389Gly polymorphism is known to affect the interaction between the receptor and a downstream G-protein (Mason et al. 1999), raises the intriguing possibility that Gly389 homozygotes respond differently to beta blockers.

In summary, we have shown both significant heritability (~40%) of resting heart rate and a significant association between β1 adrenergic–receptor genotype and heart rate. The extent to which polymorphisms in this gene influence susceptibility to and progression of heart failure and other cardiovascular morbidity and mortality remains to be determined.

Acknowledgments

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Electronic-Database Information

The URL for data in this article is as follows:

Lab of Statistical Genetics at Rockefeller University, ftp://linkage.rockefeller.edu/software/eh (for the EH program)

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