Haplotypes of the beta-2 adrenergic receptor associate with high diastolic blood pressure in the Caerphilly prospective study

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Objectives **Current evidence demonstrates that both genetic and environmental factors influence blood pressure. The sympathetic nervous system is a key player in blood pressure control and functional genetic variants of the beta-2 adrenergic receptor (B2AR) have been identified and implicated in the pathogenesis of hypertension. The present study aimed to determine the effects of common haplotypes of the *B2AR* gene upon blood pressure in the Caerphilly Prospective Study.**

Design **Two thousand five hundred and twelve men (aged 45–59 years) participated in the study. We selected individuals in the upper ($n = 347$) and lower ($n = 279$) quintiles of the diastolic blood pressure distribution fixed at two time points [phase 2 (1984–88) or phase 3 (1989–93)] as cases and controls.**

Methods **We analysed two functional polymorphisms (Arg16Gly and Gln27Glu) of *B2AR* and their haplotypes.**

Results **We found a higher risk of hypertension in individuals homozygous for the Gln27 compared to those individuals homozygous for Glu27 [odds ratio (OR) = 1.94; 95% confidence interval (CI) = 1.34–2.81; $P = 0.001$]. Three haplotypes (Gly16Gln27, Gly16Glu27 and Arg16Gln27) were present in both quintile groups. Logistic regression analysis showed that haplotypes with a Gln27 allele (Gly16Gln27 and Arg16Gln27) conferred a significantly higher risk for hypertension than the Gly16Glu27 haplotype (OR = 1.55; 95% CI = 1.11–2.17, OR = 1.37; 95% CI = 1.04–1.81; $P = 0.009$ and $P = 0.027$, respectively). However, there was no evidence to support a statistically significant difference in odds ratios for the Gly16Gln27 and Arg16Gln27 haplotypes ($P = 0.477$), suggesting that it is the Gln27 allele alone, rather than any haplotype, which best explains the association.**

Conclusions **In a prospectively studied Caucasian male cohort, high diastolic blood pressure was associated with *B2AR* haplotypes containing the pro-downregulatory Gln27 variant.** *J Hypertens* **24:471–477 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Hypertension affects 1 billion people worldwide and is implicated in 7.1 million deaths each year from ischaemic heart disease and stroke (http://www.who.int/en/index.html). Several strands of evidence point to genetic and environmental influences upon blood pressure [1]. To elucidate the genes implicated in hypertension, candidate gene and genomic screening strategies employing family-based linkage analysis and population association designs are underway.

The sympathetic nervous system influences cardiac output, vascular tone, renal sodium reabsorption and renin release. It is therefore an excellent system from which to derive candidate genes for hypertension because it has been implicated in the enhanced vascular responsiveness observed in hypertensive individuals. The beta-2 adrenergic receptor (B2AR) mediates vasodilatation, increases cardiac output [2] and may influence aortic compliance.

Several single nucleotide polymorphisms (SNPs) of the beta-2 adrenergic receptor gene (*ADRB2*) have been shown to affect B2AR expression and regulation both *in vitro* and *in vivo* [3–6]. The variants that affect B2AR regulation include a pro-downregulatory substitution of

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glycine (Gly) for arginine (Arg) at amino acid 16 and the replacement of downregulation-resistant glutamic acid (Glu) for pro-downregulatory glutamine (Gln) at amino acid 27 [3,7]. A regulatory 19-amino acid peptide encoded by a short open reading frame in the 5′ upstream region of the *ADRB2* gene has also been identified. Genetic variants of this peptide, denoted the B2AR upstream peptide (5′ BUP), have been shown to alter receptor expression via mRNA translation [8].

There is some evidence to support a functional physiological role for these variants. Normotensive individuals homozygous for the Gly16 allele have been found to have a blunted fall in peripheral vascular resistance when infused with the B2AR agonist salbutamol compared to Arg16 homozygotes [9]. Furthermore, homozygotes for Glu27 have a higher maximal venodilation in response to the B2AR agonist isoproterenol compared to those homozygous for Gln27 [10].

However, association studies on *B2AR* polymorphisms have produced conflicting results in essential hypertension. Association between the pro-downregulatory Gly16 allele and hypertension has been found in African-Caribbeans [11] and Caucasian-Americans [12,13]. Both the Gly16 and Gln27 alleles have been found to be associated with hypertension in Han Chinese [14]. However, an American study reported association with Gly16 and Glu27 [13], a Japanese study found association with Gln27 but not Gly16 [15] and a Norwegian study found the Arg16 allele to be at a significantly higher frequency among offspring of two hypertensive parents compared to offspring of two normotensive parents [16]. In addition, there have been negative studies reported in Europeans [17], black and white Americans [18,19], Italians [20] and black africans [21].

These divergent results may have arisen from unrecognized haplotype effects because these studies were limited to investigation of individual SNPs. To address this, we conducted a study to determine the effects of common haplotypes of the *ADRB2* gene upon blood pressure in the Caerphilly Prospective Study (CaPs). This major UK epidemiological study has followed the cardiovascular related outcomes of 2512 men over 20 years. To maximize the statistical power of the study, we selected individuals from the extremes of the diastolic blood pressure distribution and used blood pressure measurements taken at two time-points to avoid the effects of regression to the mean.

Methods

Subjects

In the period 1979–83, the Caerphilly Prospective Study recruited 2512 white males aged 45–59 years when first examined [22]. The Medical Research Council Epidemiology Unit in Penarth conducted the study. Following ethical approval, recruitment was via the electoral roll and primary care clinics. Fully informed consent was obtained from all participating individuals. The participants were subsequently followed up for 20 years, and they are still being assessed, with the defined aim of identifying the risk factors for cardiovascular disease. Clinical examination included age, height, weight and blood glucose levels. Trained observers measured blood pressure using a random zero sphygmomanometer three times consecutively with the participants in the seated position. Phase 5 of the Korotkoff sound was taken as diastolic blood pressure. The mean of three blood pressure measurements was used for analysis. Current treatment history with anti-hypertensive medications (including class and type), previous diagnosis of raised blood pressure and body mass index (BMI) were recorded at each follow-up point.

Hypertensive patients were screened for the presence or absence of secondary hypertension by a careful history, physical examination, blood chemistry and urinalysis. Patients with documented or suspected secondary hypertension were excluded from the study cohort.

For this study, we selected men in the upper and lower quintiles of the diastolic blood pressure distribution at phase 2 (1984–88) or phase 3 (1989–93). Diastolic blood pressure was chosen as the phenotype because systolic blood pressure increases with age, mostly as a result of stiffening of large arteries with increased pulse wave velocity [23]. Therefore, systolic blood pressure reflects, to a lesser extent than diastolic blood pressure, the primary mechanism of hypertension, namely the increase of peripheral vascular resistance occurring in the small resistance vessels [24]. The effect of blood pressure misclassification due to regression to the mean was minimized by including only those individuals who were in the upper or lower quintiles of diastolic blood pressure in one phase and were in the upper or lower 40% of the diastolic blood pressure distribution at the other phase. Men classified as on 'anti-hypertensive therapy' were excluded *a priori* from the lower quintile of the blood pressure distribution.

Selecting individuals from the upper and lower tails of a quantitative distribution for genetic analysis is known as selective genotyping [25,26] and has been shown to increase power for detecting a trait-influencing locus because most of the information lies in the extreme tails of the distribution [27–29]. Our study closely follows previous guidelines that recommend 'where possible, selecting a larger population, such as a population studied in an epidemiological survey, and making a selection from the extremes' [30].

Genotyping

Drysdale *et al.* [8] demonstrated that two SNPs, Arg16Gly (46A/G) and Gln27Glu (79G/C), are the haplotype

tagging SNPs for this gene in Caucasian populations (i.e. the SNPs that require genotyping to provide full haplotype information). Subsequent analysis using the SNPtagger program [31] to analyse data from the NCBI (http://www.ncbi.nlmn.nih.gov/) of 95 Caucasian individuals with *ADRB2* SNP data (population id 914, HG_BONN_CNS_SNPS-euro96 EUROPE) confirmed that Arg16Gly and Gln27Glu polymorphisms capture 90% of the haplotypes of this gene.

Both SNPs were genotyped in the CaPS, using a nested polymerase chain reaction approach due to limited yields and DNA quality and were genotyped using DASH [32] technology. The primers used for the un-nested amplification were: 5′-CAG AGC CCC GCC GTG TGT CC-3′ (sense) and 5′-CCA CCA CAC ACA CCT CGT CC-3′ (anti-sense), using a 50°C annealing temperature. This primary product served as the template for amplification of both SNPs due to their close proximity. The primers used for the Arg16Gly polymorphism were 5′-GCG CTT TCT TGC TGT CAC CCA A-3′ and 5′-TCG TGG TCC GGC GCA TGG CTT-3′ and 5′-CGC CGG ACC ATG ACG TTA CGC A-3′ and 5′-CCA CCA CAC ACA CCT CGT CC-3′ for Gln27Glu. Genotyping was performed using the genotyping platform dynamic allele specific hybridization (DASH) according to manufacturers recommendations [32]. The probe sequences were 5′-ATG GCT TCT ATT GGG TG-3′ and 5′-ATG GCT TCC ATT GGG TG-3′ for Arg16Gly and 5′-GTC CCT TTC CTG CGT AA-3′ and 5′-GTC CCT TTG CTG CGT AA-3′ for Gln27Glu. To verify the DASH genotyping data, we performed direct sequencing (both strands) on 200 samples that were randomly selected (approximately 32% of the population studied).

Statistical analysis

Descriptive data are presented as mean ± SD or median (10th to 90th percentile). Continuous variables were compared using Student's *t*-test if normally distributed, and otherwise using the Mann–Whitney *U*-test. Frequencies were compared using chi squared test. Calculations were performed with the SPSS statistic software package, version 11.5 (SPSS Inc., Chicago, Illinois, USA) and STATA (Stata Statistical Software, Release 8; Stata Corp., College Station, Texas, USA).

A likelihood ratio chi-squared statistic was used to determine Hardy–Weinberg equilibrium (HWE). Phased haplotypes could be determined exactly because the Arg16Glu27 haplotype does not exist in our population. Confirmation of this was obtained by the Expectation Maximization estimation of phased haplotypes using HAPLIKE software (http://www.well.ox.ac.uk/~gbenga/HAPLIKE). The likelihood ratio statistic was used to compare the genotype and haplotype frequencies between the upper and lower quintile groups. The effect of the genotypes at each marker and the haplotype effects were modelled using logistic regression and an odds ratio (OR) was used to measure the size of effect. To reduce the degrees of freedom of the haplotype test, we assumed an additive model on the log-odds scale. We also tested for indirect association using a logistic regression analysis of the number of copies of the Gly16 and Gln27 alleles, thus minimizing the degrees of freedom of the test as recently recommended [33].

Increases in both BMI and age are associated with hypertension and plasma glucose levels differed between the quintile groups. All analyses were adjusted for the subject's age at phase 2, mean BMI (measured at phases 2 and 3) and plasma glucose at phase 3 by including these as covariates in the regression analysis.

Power calculations were conducted assuming a disease-causing allele frequency of 0.42 (Arg16 allele) and 0.62 (Gln27allele). Testing each marker for direct association, the present study has a power of over 80% to detect an OR as low as 1.46 (Arg16Gly) or 1.5 (Gln27Glu). Power calculations were also conducted assuming the markers were tagging SNPs for the *ADRB2* gene using the framework from Chapman *et al.* [33]. Assuming the disease-causing haplotype has a 40–60% frequency in the population and a modest $r^2 = 0.4$ (as exists between these loci), the study has 80% power to detect an OR of at least 1.8.

Results

Demographics of the Caerphilly Prospective Study

A total of 626 men were studied. Table 1 shows the clinical characteristics of the high blood pressure and low blood pressure subjects. Systolic blood pressure and pulse pressure were significantly higher in the upper quintile group at both phases 2 and 3.

Hypertensive subjects were slightly younger compared to controls [difference 0.7 years; 95% confidence interval (CI) = 0.0–1.4 years; $P = 0.042$]. Impaired fasting glucose and diabetes mellitus were more prevalent in the case group in phases 2 and 3, and blood glucose levels were significantly higher compared to controls in phase 3 (difference 0.39 mmol/l; 95% CI = 0.14–0.64 mmol/l; $P = 0.002$). Alcohol consumption did not differ between cases and controls. BMI was found to be higher in the hypertensive group (mean difference 2.8 kg/m^2; 95% CI = 2.2–3.3 kg/m^2; $P < 0.001$) and a higher proportion were found to be obese (defined as a body mass index of 30 kg/m^2 or more) [34] at both phases. In phase 2, 102 (29%) and, in phase 3, 161 (46%) of the hypertensive subjects received pharmacological anti-hypertensive therapy.

Genetic and logistic regression analysis

Genotype frequencies were found to be in HWE at the Arg16Gly locus, but not at the Gln27Glu locus due to

Table 1 Baseline characteristics of the Caerphilly study population

	Phase 2		Phase 3	
	High blood pressure ($n = 347$)	Low blood pressure ($n = 279$)	High blood pressure ($n = 347$)	Low blood pressure ($n = 279$)
Age (years)	56.6 ± 4.4*	57.3 ± 4.5	61.7 ± 4.4*	62.4 ± 4.5
Systolic blood pressure (mmHg)	165.6 ± 22.1***	126.5 ± 15.0	163.0 ± 20.2***	127.0 ± 17.9
Diastolic blood pressure (mmHg)	99.1 ± 7.7	70.1 ± 6.4	96.8 ± 7.6	67.7 ± 7.1
Pulse pressure (mmHg)	66.5 ± 19.5***	56.7 ± 15.0	66.2 ± 17.6***	59.3 ± 16.4
Body mass index (kg/m^2)	27.2 (23.7–32.6)***	24.9 (21.0–28.9)	27.8 (23.5–32.6)***	25.0 (21.1–29.2)
No. of obese subjects	86/342***	17/278	94/342***	18/278
Glucose metabolism				
Fasting glucose (mmol/l)	5.42 ± 1.35	5.27 ± 1.24	5.81 ± 1.68*	5.42 ± 1.37
Normal fasting glucose	234***	230	193***	205
Impaired fasting glucose	79	31	103	50
Diabetes mellitus				
Alcohol intake (drinks/day)	16	12	30	13
None	49	35	80	64
0.1–1.0	29	30	12	20
> 1.0	169	214	255	195

Data are expressed as mean ± SD. Body mass index (BMI) data are expressed as median (10th to 90th percentile), height, weight and fasting blood glucose measurements were not available for all individuals. A fasting plasma glucose of below 5.6 mmol/l was defined as normal, impaired fasting glucose was defined as fasting plasma glucose between 5.6–6.9 mmol/l, and diabetes mellitus was defined as a fasting glucose concentration at or above 7.0 mmol/l [23]. In the glucose metabolism and alcohol intake sections, the numbers of individuals are listed. Groups were compared within the phases by Student's *t*-test, the Mann–Whitney *U*-test (BMI) and the chi-squared test (number of obese subjects; data on glucose metabolism). $^*P < 0.05$; $^{***}P < 0.001$.

Table 2 Genotype frequencies of the *ADRB2* gene in high blood pressure and low blood pressure groups and odds ratios adjusted for subject's age at phase 2 and mean body mass index from phases 2 and 3

	Frequency (%)				
Genotype	High blood pressure	Low blood pressure	OR	95% CI	*P*-value
Arg16Gly					
Arg16Arg	77 (22.2)	53 (19.0)	1.30	0.92–1.82	0.13
Arg16Gly	158 (45.5)	127 (45.5)	1.14	0.86–1.50	0.36
Gly16Gly	112 (32.3)	99 (35.5)	1.00		
Total	347	279			
HWE *P*-value	0.14	0.28	Overall $P = 0.31$		
Gln27Glu					
Gln27Gln	174 (50.1)	115 (41.2)	1.94	1.34–2.81	0.001
Gln27Glu	131 (37.8)	116 (41.6)	1.46	1.00–2.12	0.048
Glu27Glu	42 (12.1)	48 (17.2)	1.00		
Total	347	279			
HWE *P*-value	0.03	0.06	Overall $P = 0.0013$		

OR, Odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

excess homozygosity (Table 2). Such deviation was apparent amongst both high blood pressure and low blood pressure groups. It is known that prevalence of hypertension varies with age and BMI and hypertensives in the present study had much higher levels of fasting plasma glucose. Accordingly, all analyses were adjusted for age, BMI and fasting plasma glucose. In the analysis of genotype data (Table 2), the Gln27Glu locus was associated with high diastolic blood pressure (DBP) ($P = 0.001$). In particular, there was a significantly higher risk of hypertension associated with the CC genotype (homozygous for Gln27) compared to the GG genotype (homozygous for Glu27) (OR = 1.94; 95% CI = 1.34–2.81; $P = 0.001$).

Because the two SNPs are in linkage disequilibrium (LD) ($D' = 1$, $P < 0.01$, $r^2 = 0.4$), their haplotypes were examined. We found a significant difference in haplotype frequencies between cases and controls (Table 3; $P = 0.020$). A logistic analysis showed that both haplotypes with a Gln27 allele (Gly16Gln27 and Arg16Gln27) confer a significantly higher risk for hypertension than the Gly16Glu27 haplotype (OR = 1.55; 95% CI = 1.11–2.17; OR = 1.37; 95% CI = 1.04–1.81; $P = 0.009$ and $P = 0.027$, respectively). We may parameterize the logistic regression model to test whether the odds ratios for the two haplotypes carrying the Gln27 variant differ. A difference would suggest that the association between DBP and B2AR can only be explained by *B2AR* haplotypes. However, we found no significant difference ($P = 0.477$), suggesting that it is the Gln27 allele alone which best explains differences in DBP in this population. The analysis of the markers as tagging SNPs also showed significant evidence for an association ($P = 0.033$) but, again, the association with hypertension was strongest with the Gln27 allele (OR = 1.44; 95%

Table 3 Haplotype frequencies of the *ADRB2* gene in high blood pressure and low blood pressure groups and odds ratios adjusted for subject's age at phase 2 and mean body mass index at phases 2 and 3

	Frequency (%)				
Haplotype	High blood pressure	Low blood pressure	OR	95% CI	*P*-value
Gly16Glu27	215 (31.0)	212 (38.0)	1.00		
Gly16Gln27	312 (45.0)	233 (41.8)	1.55	1.11–2.17	0.009
Arg16Gln27	167 (24.1)	113 (20.3)	1.37	1.04–1.81	0.027
Total	694	558	Overall $P = 0.018$		

OR, Odds ratio; CI, confidence interval.

CI = 1.06–1.96; $P = 0.019$). BMI, age, the frequency of obesity or fasting plasma glucose were not related to genotypes or haplotypes (data not shown). In the course of the study, no new SNPs have been identified.

Discussion

The present study revealed an association of genetic variants of the *ADBR2* gene with hypertension in a large Caucasian male cohort, which was followed prospectively from 1984 to 1993 using a novel design exploiting the full range of the diastolic blood pressure distribution by fixing blood pressure at the upper or lower extremes at two time points. We stratified subjects according to diastolic blood pressure because systolic blood pressure is mainly the result of pulse wave velocity and early reflection of pressure waves [23]. However, individuals fixed for high diastolic blood pressure also had systolic blood pressure in the hypertensive range (Table 1). Worldwide, hypertension is not adequately controlled. The low number of subjects on pharmacological anti-hypertensive treatment is in line with previous observations from the latest NHANES report on hypertension control [35], which showed that only 58% of patients with hypertension were being treated.

Several polymorphisms of the *ADRB2* gene have been shown to affect B2AR function both *in vitro* and *in vivo*. The most commonly studied are the Arg16Gly and Gln27Glu variants. Studies performed both *in vitro* and *in vivo* provide evidence that B2AR function is influenced by the *ADRB2* genotype [5,7]. By contrast to the Arg16 and Glu27 variants, the Gly16 and Gln27 variants were found to show enhanced agonist-mediated receptor down-regulation when expressed in COS cells [7].

Vascular B2AR mediate adrenergic vasorelaxation through direct activation of vascular smooth muscle cells and, at least in part, by endothelium- and NO-dependent mechanisms [36]. The vasodilator effects of epinephrine, a B2AR agonist, partially offsets the increase in blood pressure induced by its alpha-adrenergic stimulation under conditions of mental stress, exercise and other sympathetic stimuli. A reduction of vascular beta-2 responsiveness may lead to a rise of blood pressure during sympathetic stimulation. Normotensive subjects homozygous for Gly16 show a blunted vasodilation in response to the B2AR agonists salbutamol [9] and terbutaline [12]. Healthy subjects homozygous for Glu27 show an enhanced vasodilation in response to isoproterenol compared to those homozygous for Gln27 [10].

Previously, we have described the conflicting results from studies of single SNP analysis, and suggested that haplotype analysis might aid interpretation. The high LD between Arg16Gly and Glu27Gln means that if only one SNP were causative, the other might also show association only through LD with the first. There are now some haplotype studies of *ADRB2* and hypertension available in the literature [14,37,38]. An association has been reported between stage 2 hypertension and Gly16 and Gln27 alleles and the Gly16Gln27 haplotype in Northern Han Chinese [14], supporting our observations and suggesting that this relationship may exist in different ethnic groups. The two *ADRB2* haplotype studies reported in Caucasians to date have found no association with *ADRB2* haplotypes, either with hypertension in a Polish transmission disequilibrium study of 207 families [38], or with ambulatory blood pressure in a prospective study of 571 Italians (aged 35–64 years). However, subgroup analysis in the Italian study found an association between Arg16 and Gln27 alleles and the Arg16-Gln27 haplotype and ambulatory systolic blood pressure in younger individuals (aged 35–49 years) [37]. These data suggest that haplotype studies of *ADRB2* may also have difficulty in teasing out the role of *ADRB2* in essential hypertension, although different study designs, small sample sizes and populations may be contributing to the equivocal results. The present study further found no evidence that the odds ratios for the two haplotypes carrying the Gln27 variant were different, suggesting that it is the Gln27 variant alone which is associated in this population. This suggests that the Gln27Glu variant is causative and that previous findings of an association with the Arg16Gly variant may have reflected only the high LD with Gln27Glu, but statistical methods alone will not be sufficient to unravel this story, and functional work will be required.

In the Caerphilly cohort, the hypertensive phenotype was significantly associated with pro-down regulatory Gln27

variant but not with the Gly16 polymorphism. We observed a deviation from HWE in both cases and controls for the Gln27Glu variant. Deviations in HWE may arise due to genotyping errors, non-random mating or selective pressure [39]. We genotyped this polymorphism twice using DASH and re-checked a proportion of genotypes using direct sequencing to eliminate the possibility of a genotyping error being responsible. There is no evidence from other genetic studies on this cohort of any deviation from HWE, which is against this observation arising from non-random mating [40,41]. This suggests that selective pressure is acting to maintain Hardy–Weinberg disequilibrium at this locus, supporting the hypothesis that it has a functional role. Interestingly, the study in Han Chinese also observed a deviation from HWE for both the Arg16Gly and Gln27Glu variants.

Haplotype analysis in CaPs revealed three out of four possible haplotypes (i.e. Arg16Gln27, Gly16Gln27 and Gly16Glu27), with both haplotypes carrying the Gln27 variant associated with diastolic blood pressure and with the Arg16Gln27 haplotype displaying the strongest association (OR = 1.5). The Arg16Glu27 haplotype was not observed and is very rare in Han Chinese (0.045) [14] and Italians (< 0.01) [37]. In the studies performed *in vitro* by Green *et al.* [17], the glycine at position 16 is found to clearly influence agonist-promoted down regulation of the receptor [7]. However, of interest relative to our findings is that there is a marked difference between the maximal extent of internalization of the receptor between haplotypes with and without glutamine at position 27 ($49 \pm 3\%$, $P < 0.01$) and that there are also differences in receptor distribution and conformation. These data obtained *in vitro* demonstrate there may indeed be hitherto unknown functional differences between receptors with the Gln27 variant independent of the residue at position 16. Further functional studies of haplotypes containing the Gln27 variant will be required in cultured cells naturally expressing the genotypic variations to explore whether these observations are important and have a role to play in blood pressure control. Recently, measurements of agonist-mediated venodilation in normotensive humans demonstrated that, during continuous infusion of isoproterenol, subjects homozygous for the Arg16Gln27 haplotype had a significant desensitization (i.e. reduced vasodilation) compared to subjects homozygous for the Gly16Glu27 haplotype, who did not show a B2AR desensitization over time [10].

The present study found *ADRB2* haplotypes coding for the pro-downregulatory Gln27 variant to be associated with high diastolic blood pressure in a prospectively studied male Caucasian cohort. Because only men were enrolled in the study, no conclusions can be made on the effect of *ADRB2* polymorphisms in females. These results lend further support for the candidacy of the *ADRB2* gene in blood pressure control; however, it is important that functional studies using haplotype combinations with the Gln27 variant are performed. The data also provide impetus to embark on haplotype analysis of *ADRB2* in the entire CaPS because its prospective design may allow genotypes to be related to cardiovascular morbidity and mortality outcomes.

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