Association of *ADRB2* Haplotypes with Coronary Artery Disease in Korean Patients

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Background: Beta₂-adrenergic receptor (*ADRB2*) gene variations seem to be correlated with disease progression, prognosis, and drug response to β -blockers in cardiovascular events. In this study, we investigated the genotypes and haplotypes of *ADRB2* in Korean patients and analysed their association with coronary artery disease (CAD).

Methods: One hundred five patients diagnosed with stable angina (SA), 109 patients with acute coronary syndrome (ACS), and 88 controls were enrolled. Five single nucleotide polymorphisms (SNPs) were determined at positions 46, 79, 252, 491, and 523 nucleotides, using the polymerase chain reaction and direct sequencing analysis. The haplotype reconstruction was carried out using genotype data, and analyses of the association between the genetic variation and CAD were performed.

Results: There were significant differences in the allele frequencies for the 79CG SNPs among the three groups. Relative to the control group, the distribution of 79CG genotypes was significantly different in both the SA group ($P=0.0003$) and the ACS group ($P=0.0056$). Compared with the CC genotype of 79CG, subjects with CG or GG had a higher risk of CAD (adjusted odds ratio [OR], 12.851; $P=0.014$). The frequencies of specific ACGCA, GCACC, and GGGCC haplotypes were 6.4% vs. 0%, 8.3% vs. 0%, and 6.9% vs. 0.6%, respectively, in the ACS group and controls. The GGGCC haplotype was significantly associated with CAD (adjusted OR, 12.266; $P=0.016$).

Conclusions: Although there are large ethnic differences in the distribution of *ADRB2* SNPs and their association with CAD, the 79G polymorphism and GGGCC haplotype in *ADRB2* might specifically contribute to CAD pathogenesis in Korean patients.

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INTRODUCTION

Coronary artery disease (CAD) is a complex and multifactorial disorder which involves genetic and environmental factors, including age, gender, body mass index, smoking habits, and family history, as well as accompanying disorders such as hypertension, diabetes mellitus, and dyslipidaemia [1,2]. Analyses of common single nucleotide polymorphisms (SNPs) at risk-associated loci to assess genetic predisposition to CAD suggest that several genetic factors may contribute singly and/or in combination to disease pathogenesis [3].

Beta₂-adrenergic receptors (*ADRB2*) are cell-surface receptors present in multiple tissues which activate adenylyl cyclase by coupling to guanine nucleotide binding proteins (G proteins) [4]. In the heart, *ADRB2* receptors are located on the myocardium, coronary artery, and pre-synaptically on sympathetic nerve terminals, where they mediate sympathetic activity [5]. *ADRB2* mediates increased myocardial inotropism and chronotropism and regulates coronary vasodilation [5–7]. Several studies have investigated possible associations between *ADRB2* genotypes and various cardiovascular diseases, including congestive heart failure [8], myocardial infarction [9,10], vasospastic angina [11], and hypertension [12,13].

The *ADRB2* gene is an intronless gene of 1,239 nucleotides located on chromosome 5q31–32 [14]. SNPs in the *ADRB2* gene can cause amino acid changes that potentially alter receptor function, and these polymorphic receptors show different pharmacological properties. Genetic polymorphisms of the *ADRB2* gene have been reported to be disease modifiers in cardiovascular disease, obesity, ischaemic stroke, and type 2 diabetes mellitus [15–18].

The aim of the present study was to identify common *ADRB2* polymorphisms and haplotypes associated with major cardiovascular events in the Korean population.

MATERIALS AND METHODS

1. Patients

Two groups of patients with cardiovascular disease in

Samsung Medical Center were enrolled in this study: 105 patients with stable angina (SA) and 109 patients with acute coronary syndrome (ACS). Standard definitions were used to diagnose SA and ACS, with either myocardial infarction or unstable angina based on coronary angiography, exercise tests, or imaging studies. Stable angina was defined as the presence of effort angina consistent with coronary computed tomography, or evidence of exercise-induced ischaemia by treadmill or cardiac perfusion testing in a patient with known CAD. The control group consisted of 88 unrelated individuals who underwent medical check-ups at the Health Promotion Center of Samsung Medical Center. They had normal electrocardiographs, with no history of heart disease and no chest pain. The current study was approved by the Samsung Medical Center Institutional Review Board (2010-05-071).

2. SNP Selection and Genotyping

The genotypes of five common polymorphisms within the *ADRB2* coding region associated with functional SNPs were as follows: 46AG (Arg16Gly, rs1042713), 79CG (Gln27Glu, rs1042714), 252GA (Leu84Leu, rs1042717), 491CT (Thr164Ile, rs1800888), and 523CA (Arg175Arg, rs1042718). Genomic DNA was isolated from peripheral blood mononuclear cells using a Wizard Genomic DNA Purification kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. The coding exons of the *ADRB2* gene were amplified by the polymerase chain reaction (PCR) using primers designed by the authors (available upon request). Cycle sequencing was performed, using a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA), on an ABI 3100 Genetic Analyzer (Applied Biosystems).

3. Statistical Analysis

Deviation from the Hardy-Weinberg equilibrium was tested in all subjects using the permutation version of the exact test. Linkage disequilibrium (LD) mapping was carried out using the Estimating Haplotype software program (<http://linkage.rockefeller.edu/ott/eh.htm>).

The pairwise LD coefficients among the five SNPs were calculated and the extent of disequilibrium was expressed in terms of D' and r^2 . Analyses of associations between the groups were carried out using the chi-square test and Fisher's exact test with Bonferroni's correction. Haplotype frequencies were estimated by a Bayesian algorithm using the Markov chain Monte Carlo technique. The odd ratios (OR) are given with 99.64% confidence intervals (CI) and two-sided P -values. Multi-variate logistic regression analysis was also used to adjust for the effects of co-variables (age, gender, and lipid profile status) associated with CAD. A P -value of less than 0.05 was considered significant. All analyses were performed using the SAS/Genetic ver. 9.1 (SAS Institute Inc., Cary, NC, USA) module.

RESULTS

1. General Characteristics of the Subjects

The clinical and laboratory characteristics of the patients are summarised in Table 1. Patients with CAD were older than the control group, predominantly male, and had a higher level of triglycerides and a lower level of high density lipoprotein cholesterol. However, total cholesterol and low density lipoprotein cholesterol levels were lower in patients with CAD than in the control group, probably

because of the use of lipid-lowering drugs.

2. Allele Frequencies and Genotype Distribution for the Five *ADRB2* SNPs

The genotype distributions were consistent with Hardy-Weinberg equilibrium expectation in all patients and groups (combined values: $P=1.0$ for 46AG, $P=0.1433$ for 79CG, $P=0.6919$ for 252GA, and $P=0.5114$ for 523CA). All individuals had the CC genotype for 491CT. Table 2 compares the distribution of allele and genotype frequencies for each polymorphism in the present study with results from previous studies. The distribution of the 79CG genotypes was significantly different between the CAD groups and the control group (SA vs. control, $P=0.0003$; ACS vs. control, $P=0.0056$). Compared with the CC genotype of 79CG, subjects with CG or GG had a higher risk of CAD (adjusted OR, 12.851; 95% CI, 1.681 to 98.265; $P=0.014$). Among the three groups, there were no significant differences in the allele or genotype frequencies for the other four SNPs.

3. *ADRB2* Haplotype Analysis

The five SNPs were in strong LD. Table 3 summarises the D' values, r^2 values, and P -values for pair-wise LD. The haplotype distributions of the *ADRB2* gene corresponding to the 46, 79, 252, 491, and 523 SNPs were

Table 1. Clinical and laboratory characteristics of the patients with CAD (SA and ACS groups) and the control group

Characteristic	CAD patients		Control group	P -value* (CAD vs. control)
	SA group	ACS group		
Age (yr)	63.1±10.5	60.2±13.1	56.4±9.8	0.0003
Gender (male:female)	77:28	77:32	50:38	0.0146
Total cholesterol (mg/dL)	177.6±46.7	170.7±41.5	193.3±34.9	0.0013
Triglycerides (mg/dL)	167.4±106.1	151.9±124.0	125.1±65.3	0.0134
Low density lipoprotein cholesterol (mg/dL)	118.7±40.4	106.8±37.0	125.3±34.4	0.0189
High density lipoprotein cholesterol (mg/dL)	46.9±11.9	48.1±27.4	54.6±14.7	0.0063
Use of beta-blockers	60 (57.1)	66 (60.6)	-	
Use of ACE inhibitors or ARBs	54 (51.4)	76 (69.7)	-	
Use of statins	76 (72.4)	81 (74.3)	-	

Values are presented as mean±SD or number (%).

Abbreviations: CAD, coronary artery disease; SA, stable angina; ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

*Data were analysed by the independent sample t-test or Fisher's exact test.

Table 2. Allele and genotype frequencies of five SNPs in the *ADRB2* gene in this study compared with previous studies related to ischaemic heart disease

Nucleotide locus	SNP ID	Allele (amino acid change)	Genotype	Frequencies							
				This study		Asian HapMap*	Sotoodehnia et al. [19]	Leineweber et al. [15]	Cresci et al. [29]	Park et al. [11]	
				Controls (N=88)	SA (N=105)	ACS (N=109)	(CHB+CHD +JPT)	Caucasians (N=520)	Caucasians (N=2,072)	African Americans (N=601)	Koreans (N=82)
46	rs1042713	A/G		0.659/0.341	0.562/0.438	0.601/0.399	0.531/0.469	0.376 /0.624	0.199 /0.801		0.51/0.49
		(Arg>Gly)	AA/AG /GG	0.466/0.386 /0.148	0.314/0.495 /0.191	0.330/0.541 /0.128	0.279/0.503 /0.218	0.171/0.413 /0.415	0.148/0.482 /0.370	0.273/0.489 /0.238	0.220/0.573 /0.207
79	rs1042714	C/G		0.994/0.006	0.900/0.100	0.913/0.087	0.899/0.101	0.571 /0.429	0.814 /0.186		0.91/0.09
		(Gln>Glu)	CC/CG /GG	0.989/0.011 /0	0.809/0.181 /0.010	0.844/0.138 /0.018	0.809/0.180 /0.011	0.362/0.431 /0.208	0.344/0.493 /0.163	0.680/0.283 /0.038	0.829/0.159 /0.012
252	rs1042717	A/G		0.324/0.676	0.319/0.681	0.298/0.702	0.364/0.636				
		(Leu>Leu)	AA/AG /GG	0.136/0.375 /0.489	0.114/0.410 /0.476	0.064/0.468 /0.468	0.143/0.443 /0.415				
491	rs1800888	C/T		1.0/0	1.0/0	1.0/0	0.997/0.003				
		(Thr>Ile)	CC/CT /TT	1.0/0/0	1.0/0/0	1.0/0/0	0.994/0.006 /0	0.981/0.019 /0			
523	rs1042718	A/C		0.324/0.676	0.309/0.691	0.303/0.697	0.372/0.628				
		(Arg>Arg)	AA/AC /CC	0.136/0.375 /0.489	0.114/0.391 /0.495	0.073/0.459 /0.468	0.150/0.443 /0.407				

Abbreviations: SNP, single nucleotide polymorphism; SA, stable angina; ACS, acute coronary syndrome; CHB, Han Chinese in Beijing, China; CHD, Chinese in Metropolitan Denver, CO, USA; JPT, Japanese in Tokyo, Japan.

*http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap28_B36/#search.

Table 3. Strong linkage disequilibrium between each pair of *ADRB2* single nucleotide polymorphisms

Locus	46			79			252		
	r ²	D'	P-value	r ²	D'	P-value	r ²	D'	P-value
79	0.1112	1.0	<0.0001	-	-	-	-	-	-
252	0.6955	1.0	<0.0001	0.0332	1.0	0.0016	-	-	-
523	0.5118	-0.8612	<0.0001	0.0166	0.7110	0.0250	0.6993	0.8395	<0.0001

Abbreviations: D', disequilibrium coefficient; r², squared correlation coefficient.

Table 4. Haplotype frequencies between the control group and patients with coronary artery disease (SA and ACS groups)

Haplotype	Frequencies (n, %)			P-value (control vs. SA)	OR (99.64% CI)	P-value (control vs. ACS)	OR (99.64% CI)
	Control	SA	ACS				
ACGCC	116 (65.9)	118 (56.2)	117 (53.67)	0.7225	0.6634 (0.3585–1.2278)	0.1962	0.5992 (0.3258–1.1021)
ACGCA	0	0	14 (6.42)	-	-	0.0087	-
GCACA	57 (32.4)	64 (30.5)	47 (21.56)	1.0	0.9152 (0.4820–1.7377)	0.215	0.5738 (0.2933–1.1228)
GCACC	0	3 (1.43)	18 (8.26)	1.0	-	0.0013	-
GCGCA	0	1 (0.48)	1 (0.46)	1.0	-	1.0	-
GCGCC	2 (1.14)	3 (1.43)	2 (0.92)	1.0	1.2609 (0.0867–18.3311)	1.0	0.8056 (0.0431–15.0700)
GGGCA	0	0	4 (1.83)	-	-	1.0	-
GGGCC	1 (0.57)	21 (10.00)	15 (6.88)	0.0010	19.4444 (0.9700–389.7898)	0.0224	12.9310 (0.6283–266.1382)

Significant P-values and ORs are indicated in bold characters.

Abbreviations: SA, stable angina; ACS, acute coronary syndrome; OR, odds ratio; CI, confidence interval.

similar between the SA group and control group, with the exception of GGGCC (SA vs. control: 10.0% vs. 0.6%; Table 4). However, there were significant associations between three specific *ADRB2* haplotypes and ACS: the frequencies of ACGCA, GCACC, and GGGCC haplotypes were 6.4% vs. 0% ($P=0.0087$), 8.3% vs. 0% ($P=0.0013$), and 6.9% vs. 0.6% ($P=0.0224$) for the ACS group versus the control group, respectively. The GGGCC haplotype was a significant risk factor for the development of CAD (adjusted OR, 12.266; 95% CI, 1.600 to 94.011; $P=0.016$). The GGGCA haplotype was only found in patients with ACS, although this was not statistically significant.

DISCUSSION

The present study showed significant associations between specific *ADRB2* genetic variations and CAD in Korean patients. The 79G allele of *ADRB2* was a risk factor for both SA and ACS, and the GGGCC haplotype for the 46, 79, 252, 491, and 523 SNPs was significantly

associated with a higher risk for both diseases.

Numerous clinical studies have been conducted to assess the relevance of *ADRB2* SNPs in the causation, progression, and management of CAD. Three major non-synonymous SNPs (46AG, 79CG, and 491CT) in the *ADRB2* gene have been mainly studied for their association with various cardiovascular diseases, including hypertension, ventricular arrhythmia, myocardial infarction, and sudden cardiac death [15,19–21]. However, the results of those studies were not consistent. Heckbert et al. [10] showed that 79G allele carriers had a lower risk of coronary events than 79C homozygotes among more than 5,000 elderly patients. Schurks et al. did not find an association of any single *ADRB2* SNP with myocardial infarction, ischaemic stroke, or death due to cardiovascular disease in a large study of over 25,000 Caucasian women [22]. Meta-analyses for the 46GA and 79CG alleles showed no significant association with ischaemic heart failure risk [23]. Park et al. [11] reported that the 79CC genotype was associated with vasospastic

angina in Korean patients.

The present study showed that 79G carriers with CG or GG genotypes had a greatly increased risk for CAD. Differences in the study design and characteristics of participants among studies might influence the results of these analyses. In particular, there are ethnic differences in allele and genotype frequencies of SNPs in *ADRB2*, especially 46AG and 79CG. The 79CG allele frequency in Asians is significantly different from that in Caucasians. The C allele frequency of 79CG is 0.533 in HapMap-CEU, 0.825 in HapMap-YRI, 0.878 in HapMap-CHB, and 0.920 in HapMap-JPT. Only one (0.6%) 79G allele was found among the 88 control patients in this study, consistent with the reported allele frequency in Asians.

Although the 46AG allele has been reported in many previous studies to alter functional properties of the β_2 -adrenergic receptor and to be associated with CAD [24], there was no significant association in the Korean patients in this study. Although Ile164 polymorphism is also associated with earlier and more aggressive CAD and affects prognosis in patients with severe CAD in Caucasian populations [25], the Ile164 allele was not detected in the Korean population of this study. The reported frequency of Ile164 polymorphism is 1% in Caucasians, less than 2% in Africans, and non-polymorphic in the Chinese [26]. Based on HapMap data, the Ile164 allele has a minor allele frequency of less than 0.012% in Asians. Different distributions of allele frequencies might lead to discrepancies in results among different ethnic groups. In addition, CAD is caused by multiple influencing factors, and inconsistent results may reflect various pathogeneses of the disease.

The present study suggests that subjects harbouring the GGGCC haplotype of the *ADRB2* gene have a significantly increased risk of SA and ACS. The ACGCA and GGGCA haplotypes are rare in Koreans and were only identified in the ACS group of this study. ACGCC was the most common haplotype in this study, and ACGCC and GCACA haplotypes accounted for more than 98% of the control group. Wild-type *ADRB2* contains Arg16-Gln27-Thr164 [15], corresponding to the ACGCC haplotype in this study. The Gly16-Gln27-Thr164 haplotype is

associated with a reduced risk of incident myocardial infarction in Caucasian women and shows agonist-promoted down-regulation [22,24]. The total frequencies of haplotypes GCACA, GCACC, GCGCA, and GCGCC in the present study (which correspond to Gly16-Gln27-Thr164) were not different between the control group and CAD groups, with the exception of GCACC which was predominant in the ACS group. This might be due to the male predominance and combination with additional SNPs of 252A and 523C in this group.

The specific GGGCC haplotype might contribute to CAD in Korean patients by causing an alteration in gene expression or a specific modification of protein function. Sivapalaratnam et al. [27] previously reported increased *ADRB2* expression in circulating monocytes of patients with CAD. The 79CG polymorphism has no considerable influence on the functional activity of *ADRB2* in the heart [24], although multiple gene-gene and gene-environmental factor interactions cannot be excluded.

There were several limitations in the present study. Firstly, this study was performed in a relatively small number of cases and controls, which might reduce the statistical power. Furthermore, our samples were not matched for age, gender, and other risk factors. Therefore, a larger matched case-control study should be performed to establish the association between the *ADRB2* gene variations and CAD risk. Secondly, a number of other genetic and environmental factors can influence CAD susceptibility. We could not assess the gene-gene and gene-environmental factor interactions to modify the effect of *ADRB2* polymorphisms to CAD. In addition, no functional evaluations to elucidate the mechanism of the *ADRB2* polymorphisms in CAD were conducted.

CAD is one of the leading causes of morbidity and mortality worldwide. Genetic susceptibility is claimed to account for 50% of its predisposition [28]. Many efforts have been made to elucidate the genetic contributors to the pathogenesis of CAD. However, there are large ethnic and geographical differences among studies, and data on the genetic factors associated with CAD are still inconclusive. Identification of the genetic background of CAD in Korean patients is very important with respect to

CAD pathogenesis, disease prevention, and individualised management specific to this ethnic population. Although the present data require further confirmation in larger patient populations, the data indicate that the specific 79G polymorphism and GGGCC haplotype in *ADRB2* might contribute to the pathogenesis of CAD in Korean patients.

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한국인의 *ADRB2* 유전자 일배체형과 관상동맥병의 연관성 분석유은형¹ • 이가연² • 이수연³ • 전은석²¹건양대학교 의과대학 진단검사의학과, 성균관대학교 의과대학 삼성서울병원 ²순환기내과, ³진단검사의학과

배경: 베타 2-아드레날린 수용체(Beta₂-adrenergic receptors, *ADRB2*)의 유전자 변이는 심혈관질환의 진행, 예후 및 베타 차단제에 대한 약물 반응과 관련이 있는 것으로 여겨져 왔다. 본 연구에서는 한국인의 *ADRB2* 유전자형과 일배체형을 조사하고 관상동맥병과의 연관성을 분석하였다.

방법: 105명의 안정형심증 환자군, 109명의 급성관동맥증후군 환자군, 88명의 대조군을 대상으로, 중합효소연쇄반응과 직접염기서열법을 이용하여 46, 79, 252, 491, 523번째 뉴클레오타이드의 단일 뉴클레오타이드다형태(single nucleotide polymorphisms, SNPs)를 분석하였다. 유전자형을 바탕으로 일배체형을 구성하고, *ADRB2* 유전자 변이와 관상동맥병의 연관분석을 시행하였다.

결과: 세 그룹 간에 79CG SNP의 대립인자 빈도는 유의한 차이를 보였다. 79CG 유전자형의 분포도 안정형심증 환자군과 대조군($P=0.0003$), 급성관동맥증후군 환자군과 대조군($P=0.0056$) 사이에서 유의하게 달랐다. 79CG의 CC 유전자형에 비해 CG 또는 GG 유전자형일 때 관상동맥병의 위험도가 증가하였다(adjusted odds ratio [OR], 12.851; $P=0.014$). 또한 ACGCA, GCACC 그리고 GGGCC 일배체형은 급성관동맥증후군 환자군과 대조군에서 각각 6.4%와 0%, 8.3%와 0%, 6.9%와 0.6%의 빈도를 보였으며, 특히 GGGCC 일배체형이 관상동맥병과 연관성이 높았다(adjusted OR, 12.266; $P=0.016$).

결론: *ADRB2* SNP의 분포와 관상동맥병과의 연관성은 인종 간의 차이가 있으나 한국인에서 *ADRB2*의 79G 다형성과 GGGCC 일배체형은 관상동맥병과 유의한 연관성을 보였다.

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