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Association of the Gene Polymorphisms of Platelet Glycoprotein Ia and IIb/IIIa with Myocardial Infarction and Extent of Coronary Artery Disease in the Korean Population

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Platelet membrane receptor glycoproteins (GP) are essential for the platelet activation process, and the genetic polymorphisms in the genes that encode platelet glycoproteins have been proposed to influence the risk of acute coronary syndrome and atherosclerosis. In this study, we investigated the role of GPIa, HPA-1 and HPA-3 polymorphisms as putative risk factors for myocardial infarction (MI) and the extent of coronary artery disease. We selected 1,073 subjects who underwent coronary angiography; 242 had normal or minimal coronary atherosclerosis, and 831 patients had significant coronary artery disease (CAD). The genotype was determined by the methods of single base extension for C807T/G873A polymorphisms of GPIa, and restriction fragment length polymorphism for HPA-1 and HPA-3. The C807T and G873A polymorphisms of GPIa showed complete linkage in the Korean population. For HPA-1 gene polymorphism, only the HPA-1a/a ($Pl^{A1/A1}$) genotype was observed in 192 selected subjects from our study population. The distribution of GPIa (C807T/G873A) and HPA-3 genotypes did not differ significantly between normal subjects and CAD subjects. No significant association between MI and both gene polymorphisms was present. However, for the subgroup analysis of young male patients whose age was less than 56 years, the genotype frequency of HPA-3b/b was significantly lower in patients with MI compared to patients without a history of MI (7.5% vs. 20.0%, p=0.04). The odds ratio for HPA-3 b homozygosity versus the HPA-3a carrier was 0.32 (95% CI, 0.10- 0.99, p=0.04).

Conclusively, HPA-3 polymorphism was associated with MI in Korean individuals younger than 56 years of age, but other polymorphisms of GP, which we studied, were not associated with both the extent of coronary atherosclerosis or MI.

Key Words: Polymorphism, genetics, platelet membrane glycoproteins, myocardial infarction, coronary artery disease, Koreans

INTRODUCTION

Platelet adhesion, activation, and aggregation are prominent features in thrombus formation, leading to acute coronary syndrome and a rapid progression of atherosclerosis.[1-3] Platelet membrane receptor glycoproteins (GP) are essential for the platelet activation process,[4] and the genetic polymorphisms in the genes encoding platelet glycoproteins have been proposed to influence the risk of acute coronary syndrome and atherosclerosis.

The GPIa/IIa is a platelet collagen receptor and it plays an important role in platelet adhesion.[5] Two linked silent polymorphisms within the coding region of GPIa (C807T and G873A) have been known to be associated with the number of GPIa/IIa copies on the platelet membrane, suggesting the association with thrombotic events.[6,7] Several studies have shown the association between T807 and myocardial infarction (MI),[8,9] but the clinical significance of this variation has

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not been clearly defined yet.

Glycoprotein IIb/IIIa is another platelet membrane receptor; it functions as a receptor for fibrinogen and binds the von Willebrand factor during platelet aggregation.[4] These two glycoproteins, GPIIb and GPIIIa, are also polymorphic in humans. The human platelet antigen-1 (HPA-1) polymorphism, well known as the Pl^A GPIIIa polymorphism, arises from a single base change leading to an amino acid change at position 33 and has been extensively studied as an inherited risk factor for acute coronary syndrome.[10-12] However, the associations of HPA-1 with coronary thrombosis and atherosclerosis are inconsistent.[13] The human platelet antigen-3 (HPA-3) polymorphism results from a thymine to guanine base change that leads to the replacement of isoleucine (HPA-3a) by serine (HPA-3b) at codon 843 of GPIIb.[14] This polymorphism may potentially influence the activity of the GPIIb/IIIa complex, but the associations with acute coronary syndrome and atherosclerosis have not been completely defined yet.

We hypothesized that those gene polymorphisms of platelet GP may predispose the thrombotic events leading to a myocardial infarction and more advanced atherosclerosis. We therefore, studied the role of GPIa, HPA-1 and HPA-3 polymorphisms as putative risk factors for MI and the extent of coronary artery disease (CAD) confirmed by coronary angiography in 1,073 Koreans.

MATERIALS AND METHODS

Study population

Study subjects were patients admitted to Yonsei Cardiovascular Hospital, Seoul, Repubic of Korea, from May 1998 to November 2000. CAD patients and control subjects confirmed by angiography were recruited for our study. CAD was defined as $\geq$ 50% diameter stenosis of at least one epicardial coronary artery, and normal was defined as a maximal diameter stenosis of $<$ 20% at all epicardial coronary arteries with no history of previous or acute MI. We selected 1,073 subjects matched for age and gender according to the extent of CAD. The extent of CAD was defined by the number of involved coronary arteries in a 1-, 2-, or 3-vessel disease. Data on smoking habits, body weight and height, and previous medical history were recorded. These data were validated with reference to hospital case records. The history of MI was confirmed according to the World Health Organization (WHO) criteria for symptoms, enzyme elevations, or electrocardiographic changes. Blood samples were collected after 12 hours of fasting and were tested for total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Low-density lipoprotein (LDL) cholesterol was calculated with Friedewald formula. The protocol was approved by the Ethical Committee of Yonsei University College of Medicine, and informed written consent to participate was obtained from all patients.

Genetic analysis

Genomic DNA was purified from the peripheral leukocyte using a commercially available DNA isolation kit (WIZARD® Genomic DNA purification kit, Promega Corp., Madison, WI, USA). Two polymorphisms of GPIa were genotyped using the SNaPshot kit (PE Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions to determine the genotype. The region of interest was amplified with polymerase chain reaction (PCR) using the following primers: 5'-GTG TTT AAC TTG AAC ACA TA-3' and 5'-GAT TTA ACT TTC CCA GCT GC-3' for the C807T polymorphism, and 5'-CGA ATA CTG GGA TAA ATA CAT GC-3' and 5'-CTC AGT ATA TTG TCA TGG TTG C-3' for the G873A polymorphism of the GPIa gene. After amplification, the PCR products were incubated with 1 unit each of shrimp alkaline phosphatase (Amersham, Buckinghamshire, UK) and Exo I (New England Biolabs, Beverly, MA, USA) at 37℃ for 1 hour. An extension reaction, to determine the genotype, was carried out for 25 cycles at 96℃ for 10 seconds, 55℃ for 5 seconds, and 60℃ for 30 seconds with primers 5'-GGG GAC CTC ACA AAC ACA TT-3' for C807T and 5'-TGG GCG ACG AAG TGC TAC-3' for G873T. After the reaction with 1 unit of shrimp alkaline phosphatase, 1 μl of this product was mixed with 10 μl of deionized formamide and separated on a ABI PRISM 310

DNA sequencer (PE Applied Biosystems). Genotype was determined by GeneScan Analysis.

The HPA-1 and HPA-3 polymorphisms were determined by allele-specific restriction enzyme analysis after amplification. For HPA-1, a 266-bp sequence of the GPIIIa gene was amplified (primer sequences; 5'-TTC TGA TTG CTG GAC TTC TCT T-3' and 5'-TCT CTC CCC ATG GCA AAG AGT-3') and digested with MspI (MBI Fermentas, St. Leon-Rot, Germany). For HPA-3, a 460-bp sequence of the GPIIb gene was amplified (primer sequences; 5'-GTA AGA GCT GGG TGG AAG AAA GAC C-3' and 5'-CTC CTT AAC GTA CTG GGA AGC-3') and digested with BseGI (MBI Fermentas, St. Leon-Rot, Germany). BseGI cleaves the PCR products into 3 fragments of 171 bp, 156 bp and 133 bp for HPA-3a, and 2 fragments of 304 bp and 156 bp for HPA-3b. Digested PCR fragments were separated on agarose gel or 8% polyacrylamide gel and visualized by ethidium bromide staining and UV transillumination.

Statistical analysis

Statistical analysis was performed by using the SPSS 11.0 software (GmbH software, Munich, Germany) for Windows and a p value of less than 0.05 was considered significant. All data are presented as the mean ± SD or as a proportion. The student t-test and χ^2-test were used for analysis of the continuous and categorical variables, respectively. Allele frequencies were estimated by gene counting methods and tested for deviation from the Hardy-Weinberg equilibrium using the χ^2-test.

RESULTS

Two hundred and forty two subjects with normal coronary arteries, and 831 patients with CAD confirmed by angiography were studied. One hundred and seventy eight patients from the CAD group had a history of nonfatal MI. Baseline characteristics of the study population are presented in Table 1. The age distribution and proportion of males were quite similar, due to the fact that we selected the age and gender matched subjects according to the extent of CAD. The patients with multiple-vessel CAD had higher incidences of diabetes (22.7% for 2-vessel and 34.6% for 3-vessel) than patients with normal coronary arteries (15.6%)($p<0.05$). The proportion of smokers was higher in the CAD group compared to that of the normal coronary artery group, and HDL cholesterol was significantly lower in any CAD group compared to normal patients. Among the patients with CAD, those with MI were more often male (78.1% vs. 63.4%, $p<0.001$), younger (59.3 ± 9.3 vs. 62.6 ± 8.3 years, $p<0.001$),

Table 1. Clinical Characteristics of the Study Population

	CAD			MI		Normal
	1VD	2VD	3VD	With	Without	
No. of patients	279	285	267	178	653	242
Male/female (%)	66.7/33.3	67.7/32.3	65.2/34.8	78.1/21.9†	63.4/36.6	62.0/38.0
Mean age (y)	61.6 ± 8.5	61.9 ± 8.6	62.6 ± 8.8	59.3 ± 9.3†	62.6 ± 8.3	61.0 ± 8.9
BMI (kg/m^2)	25.1 ± 3.5	25.0 ± 3.8	24.9 ± 2.8	24.7 ± 2.8	25.1 ± 3.5	24.8 ± 3.9
Hypertension (%)	42.7	44.6	51.7	42.1	47.3	45.5
Diabetes (%)	16.6	22.7*	34.6*	24.1	24.7	15.6
Smoking (%)	42.7*	43.5*	44.6*	54.5†	40.6	32.2
Total cholesterol (mg/dl)	190.0 ± 37.0	189.9 ± 36.3	194.6 ± 44.3	193.4 ± 41.0	191.0 ± 39.0	186.0 ± 39.7
LDL-C (mg/dl)	118.9 ± 30.7	119.2 ± 33.0	120.8 ± 39.7	124.4 ± 5.6	118.4 ± 34.4	112.1 ± 35.3
HDL-C (mg/dl)	42.9 ± 10.3*	41.5 ± 10.4*	41.3 ± 11.5*	41.4 ± 0.5	42.0 ± 10.8	45.7 ± 14.9
Triglycerides (mg/dl)	148.1 ± 93.8	144.69 ± 70.9	165.8 ± 113.2	145.8 ± 90.2	154.9 ± 96.0	146.4 ± 90.3

CAD, coronary artery disease; MI, myocardial infarction; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
*$p<0.05$ compared to normal, †$p<0.05$ compared to CAD patients without MI.

and smokers (54.5% vs. 40.6%, p=0.001).

The C807T and G873A polymorphisms of GPIa showed complete linkage in our study population (D'=1.0, $p<0.0001$), and the 807T allele always accompanied the 873A allele in the entire study population. For the HPA-1 gene polymorphism, only the HPA-1a/a ($Pl^{A1/A1}$) genotype was observed in the selected 192 subjects from our study population, suggesting that this polymorphism of GPIIIa cannot be a genetic risk in the Korean population.

The genotype and allele distributions according to the extent of CAD are shown in Table 2. Within each study group, the genotype distributions were within the Hardy-Weinberg equilibrium. No significant association was observed between each genotype and cardiovascular risk factors such as age, gender, hypertension, diabetes, smoking habits, and lipid profiles (data not shown). The distribution of GPIa C807T and HPA-3 genotypes did not differ significantly between the normal and CAD group (p=0.983 and p=0.931, respectively). Also, there was no significant difference of genotype frequency according to the extent of CAD.

The relationship between the genetic polymorphism and MI are shown in Table 3; no significant association was demonstrated between them. The proportions of patients with MI were 29.8%, 37.1% and 33,1% for 1-, 2-, and 3-vessel disease, respectively (p=0.459). The subgroup analysis in young male patients below 56 years of age showed that the genotype frequency of HPA-3b/b was significantly lower in MI patients compared to the patients without a history of MI (7.5% vs. 20.0%, p=0.04). The OR for HPA-3b homozygosity versus the HPA-3a carrier was 0.32 (95% CI, 0.10-0.99, p=0.04) and the OR for HPA-3b homozygosity versus the HPA-3a homozygosity was 0.29 (95% CI, 0.09-0.96, p=0.03).

DISCUSSION

In the present study, we evaluated the potential risk of genetic variations of platelet membrane glycoproteins for CAD or MI, and have found an association between HPA-3 polymorphism and MI. However, none of the genetic variations we studied were associated with the extent of coronary atherosclerosis.

The HPA-3 polymorphism has received little

Table 2. Genotype and Allele Distribution According to the Extent of CAD

	CAD				Normal
	1 VD	2 VD	3 VD	Total	
GPIa C807T					
Genotype frequency					
807CC, n(%)	128 (45.9)	116 (40.7)	118 (44.2)	362 (43.6)	104 (43.0)
807CT, n(%)	128 (45.9)	129 (45.3)	115 (43.1)	372 (44.8)	109 (45.0)
807TT, n(%)	23 (8.2)	40 (14.0)	34 (12.7)	97 (11.7)	29 (12.0)
Allele frequency					
807C/807T (%)	0.69/0.31	0.63/0.37	0.66/0.34	0.66/0.34	0.65/0.35
HPA-3 a/b					
Genotype frequency					
HPA-3 a/a	95 (34.1)	101 (35.4)	81 (30.3)	277 (33.3)	82 (33.9)
HPA-3 a/b	133 (47.7)	143 (50.2)	140 (52.4)	416 (50.1)	118 (48.8)
HPA-3 bb	51 (18.3)	41 (14.4)	46 (17.2)	138 (16.6)	42 (17.4)
Allele frequency					
HPA-3a/HPA-3b (%)	0.58/0.42	0.61/0.39	0.57/0.43	0.58/0.42	0.58/0.42

VD, vessel disease; GPIa, platelet membrane glycoprotein Ia; HPA-3, human platelet antigen-3.

Table 3. Genotype and Allele Distribution according to the History of MI among CAD Patients

	MI		MI (male, age ≤ 55 years)	
	With	Without	With	Without
GPIa C807T				
Genotype frequency				
807CC, n (%)	81 (45.5)	281 (43.0)	24 (45.3)	43 (41.0)
807CT, n (%)	80 (44.9)	292 (44.7)	24 (45.3)	49 (46.7)
807TT, n (%)	17 (9.6)	80 (12.3)	5 (9.4)	13 (12.4)
Allele frequency				
807C/807T (%)	0.68/0.32	0.65/0.35	0.68/0.32	0.64/0.36
OR (95% CI) for MI				
807 TT vs 807 CC + 807 CT	0.76 (0.44-1.31)		0.74 (0.25-2.19)	
807 TT vs 807CC	0.73 (0.41-1.32)		0.69 (0.22-2.16)	
HPA-3 a/b				
Genotype frequency				
HPA-3 a/a	65 (36.5)	212 (32.5)	24 (45.3)	37 (35.2)
HPA-3 a/b	88 (49.4)	328 (50.2)	25 (47.2)	47 (44.8)
HPA-3 b/b	25 (14.0)	113 (17.3)	4 (7.5)	21 (20.0)
Allele frequency				
HPA-3a/HPA-3b (%)	0.61/0.39	0.58/0.42	0.69/0.31	0.58/0.42
OR (95% CI) for MI				
HPA-3b/b vs HPA-3a/a + HPA-3a/b	0.78 (0.49-1.24)		0.32 (0.10-0.99)*	
HPA-3b/b vs HPA-3a/a	0.72 (0.43-1.21)		0.29 (0.09-0.96)*	

*$p<0.05$.

interest because previous studies showed a lack of association with an increased risk of stroke or MI.[15,16] Recently, Carter et al.[17] showed that the relative risk for poststroke mortality in patients of the HPA-3 a/a and a/b genotype compared with those of the HPS-3b/b genotype are 2.42 and 2.13, respectively. This suggests a better survival rate in patients of the HPA-3b/b genotype after an ischemic stroke. The genotype distribution of HPA-3 was not different between normal subjects and patients with CAD and MI in our study group. But, subgroup analysis of younger males (≤ 55 years) showed that the patients who carry HPA-3b/b had a lower risk for MI compared to patients carrying HPA-3a/b or HPA-3a/a. The decreased risks for MI in patients of the HPA-3b/b genotype may implicate a decreased platelet activation and thrombotic tendency in patients of the HPA-3b/b genotype. The HPA3-b allele encodes a Ser instead of Ile at codon 843 of the GPIIb heavy chain, and this polymorphism lies adjacent to the binding region of PMI-1, which may be related with conformational change after ligand binding.[14] However, it was not determined whether the HPA-3 polymorphism alters platelet function or not. Further studies regarding the association between the GPIIb polymorphism and platelet function need to be clarified.

HPA-1 polymorphism has been widely studied by others in association with MI or atherosclerotic disease. A meta-analysis regarding the role of GPIIIa polymorphism demonstrated the effect of HPA-1 (pl^{A2}) on the risk of coronary artery disease in subjects below 60 years of age.[12] Although the GPIIIa polymorphism has been frequently demonstrated in Caucasians and reported to be associated with both the progression of CAD and coronary thrombosis, our study shows an absence of polymorphism for GPIIIa making it insignificant as a marker of risk for coronary artery dis-

ease in Koreans. This finding was similar to previous reports that showed quite a low prevalence of variation in Koreans and Japanese when compared to Caucasians (0.02% vs. 15%).[18,19]

There are several genetic variations of GPIa, which is the (2 subunit of major collagen receptor $\alpha_2\beta_1$. C807T (Phe^{224}) and G873A (Thr^{246}) are synonymous polymorphisms among them, and previous reports have shown a significant correlation between these polymorphisms and MI.[8,9] They found that male individuals who carry the 807T allele show a significant increase in risk for nonfatal MI. On the contrary, recent reports have shown a lack of association between the C807T genotype and MI or adverse outcomes after coronary artery stenting.[20,21] Our results also showed a lack of an association between the 807T allele and MI or coronary atherosclerosis. The C807T polymorphisms were reported to be linked with $\alpha_2\beta_1$ density on the platelet membrane with increased platelet adhesion to collagen, even though the mechanism has not been known. There are several possibilities for the lack of an association between the GPIa C807T polymorphism and CAD in our study: (1) there is lack of linkage of this synonymous polymorphism with other functional variants in the Korean population, and (2) the genetic effect of 807T needs other enhanced procoagulant responses, such as in the genetic variation of HPA-1 which shows an increased risk for thromboembolic events. It should be noted that our subjects were a selected population of patients referred for coronary angiography, and they were matched for age and gender according to the extent of CAD. The control subjects were also patients who underwent a coronary angiography in order to exclude the patients with coronary atherosclerosis and those who may have different characteristics from normal controls in the general population. Further prospective studies will be needed to clarify our results.

Conclusively, we found a significant association between the HPA-3 polymorphism and patients below 56 years of age with MI, but not with coronary atherosclerosis. The C807T/G873A polymorphism of GPIa was not associated with CAD or MI, and the genetic variation of HPA-1 was not a useful marker for genetic risk because of its low prevalence in Koreans.

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