Int J Clin Exp Med 2016;9(10):19953-19959
www.ijcem.com /ISSN:1940-5901/IJCEM0024411

Original Article

Association between platelet membrane glycoprotein polymorphisms and risk of coronary heart disease

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Received January 19, 2016; Accepted May 24, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: To investigate the association of platelet membrane glycoprotein polymorphisms (GPIaC807T, GPIbαKOZAK-5T/C, GPVIT13254/C, HPA-1a/b and HPA-2a/b) and coronary heart disease (CHD). Methods: A total of 303 patients were enrolled in this study. The patients with > 50% stenosis in one or more coronary arteries by angiography were included in the case group (150), while others with < 10% stenosis in any coronary artery were included in the control group (153). The target genes and single nucleotide polymorphisms (SNPs) were detected by improved Multiplex Ligation Detection Reaction (iMLDR). Stata 12.0 was used for data analyses. Results: Differences in genotype and allele frequency distributions of GPIaC807T were statistically significant (genotype: P=0.036, allele: P=0.017) as compared to the control group. For GPVIT13254/C, the differences in allele frequency distributions between the two groups were statistically significant (P=0.004), but not the genotype distributions (P=0.059). The genotype and allele frequency distributions of GPIbαKOZAK-5T/C, HPA-1a/b and HPA-2a/b were comparable in the two groups. Polymorphisms of GPIaC807T had the greatest influence on CHD in the additive model (OR=2.75, 95% CI: 1.18-6.71), followed by the recessive model (OR=2.48, 95% CI: 1.11-5.83) and the allele model (OR=1.52, 95% CI: 1.06-2.17). Polymorphisms of GPIbαKOZAK-5T/C were not associated with the risk of CHD in all gene analysis models. The numbers of mutant alleles were associated with coronary lesions (OR=1.36, P=0.008, 95% CI: 1.082-1.707). Logistic analysis showed that TT genotype of GPIaC807T had higher risk of CHD than CC genotype (OR=4.00, P=0.020, 95% CI: 1.24-12.88) after adjusting for gender, smoking, fasting blood glucose (FBG), triglyceride (TG) and fibrinogen (Fib). Conclusion: Polymorphisms of GPIaC807T were significantly correlated with the risk of CHD in China, and the TT genotype was independently associated with CHD. The C allele of GPVIT13254/C may increase the risk of CHD. The numbers of mutant alleles were positively correlated with the risk of CHD. However, polymorphisms of GPIbαKOZAK-5T/C, HPA-1a/b and HPA-2a/b were not associated with CHD.

Keywords: Platelet membrane glycoprotein, polymorphism, SNP, coronary heart disease, genetic association

Introduction

Cardiovascular diseases have been increasing in the highly populous countries of the developing world, including China and India [1]. China's Ministry of Health data showed that approximately 3.5 million Chinese die each year from cardiovascular disease. CHD, a serious cardiovascular disease, is the leading cause of mortality and morbidity in China [2, 3]. Platelets and thrombosis play very important roles in the atherogenesis process in CHD [4]. Platelet membrane glycoprotein receptors mediate crucial reactions in acute thrombosis and chronic processes of atherogenesis [5]. Association between polymorphisms of platelet membrane glycoprotein and CHD are an important aspect of genetic association studies of cardiovascular disease.

PIA2 polymorphism of the glycoprotein IIIa gene had a strong association with acute coronary thrombosis in patients with coronary events [6]. Systematic review also showed that PIA2 polymorphism was associated with an increased risk of coronary thrombosis [7-9]. In contrast, some studies suggested no association between PIA2 polymorphism and CHD [10, 11]. The results of these studies are inconsistent because the genes involved in the pathogenesis of CHD may belong to "minor genes", hence their effects are difficult to measure when individually studying the association of a single gene with CHD.

Table 1. PCR primer sequences

Gene	SNPs sequences	Allel	Forward primers 5'-3'	Reverse primers 5'-3'
ITGA2	rs1126643	C/T	CCTTAAAGCTACCGGCCCATGT	TTGGCCTATTAGCACCAAAACTTACC
ITGB3	rs5918	C/T	GGTAGGGCCTGCAGGAGGTAGA	TGCAATCCTCTGGGGACTGACT
GP1BA	rs2243093	C/T	TGGGAGATGGGAGTAGGGAGGA	CTGGCCACTTTGGAGACCTCAC
GP1BA	rs6065	C/T	GTCTCCTTCAACCGGCTGACCT	GAGCTTCTCCAGCTTGGGTGTG
GP6	rs1613662	G/A	GGATTGGGGGCAGCATCTTAAC	TTTCCCAGGAACCTCTGTGACC

Table 2. Demographic and clinical characteristics of study participants

Variables	Case (n=150)	Control (n=153)	*t* value	x^2 value	*P* value
Age (y)	65.70±9.40	64.90±10.00	0.717		0.237
Male (%)	116 (77.3)	66 (43.1)		36.925	0.000
BMI (kg/m^2)				0.039	0.981
Normal (< 24) (%)	84 (56.0)	84 (55.3)			
Overweight (24-28) (%)	55 (36.7)	56 (36.8)			
Obesity (> 28) (%)	11 (7.3)	13 (7.9)			
TC (mmol/L)	4.77±1.15	4.78±1.08	0.078		0.978
TG (mmol/L)	1.89±1.10	1.61±1.22	2.097		0.037
LDL (mmol/L)	2.74±1.01	2.95±0.88	1.931		0.027
HDL (mmol/L)	1.21±0.47	1.12±0.30	1.991		0.051
FBG (mmol/L)	8.43±5.04	6.87±2.40	3.450		0.001
HCY (μmol/L)	14.38±6.87	13.58±7.25	0.986		0.325
Fib (g/L)	3.53±0.99	3.03±1.03	4.307		0.013
ApoA I (g/L)	1.12±0.35	1.25±0.32	3.375		0.001
ApoB (g/L)	0.82±0.26	0.77±0.29	1.580		0.050
Smoking (%)	72 (48.0)	37 (24.2)		18.654	0.000
Family history of CHD (%)	14 (4.7)	8 (5.2)		1.895	0.169
Diabetes (%)	48 (15.8)	18 (11.8)		18.203	0.000
Hypertension (%)	69 (46.0)	66 (43.1)		0.251	0.616

Data are presented as mean (SD) or N (%), unless stated otherwise. BMI = body mass index, TC = total cholesterol, TG = triglyceride, LDL = low-density-lipoprotein, HDL = high-density lipoprotein, FBG = fasting blood glucose, HCY = homocysteine, Fib = fibrinogen, ApoA I = apolipoprotein AI, ApoB = apolipoprotein B, CHD = coronary heart disease.

The association between platelet membrane glycoprotein multiple SNPs and CHD has been rarely studied. So it is necessary to further clarify the role of platelet membrane glycoprotein polymorphisms in the pathogenesis of CHD by clinical research. In this study, we detected polymorphisms of platelet membrane glycoproteins GPIaC807T (rs1126643), GPIbαKOZAK-5T/C (rs2243093), GPVIT13254/C (rs16136-62), HPA-1a/b (rs5918) and HPA-2a/b (rs6065), and analyzed the correlation of these SNPs with the risk of CHD.

Subjects and methods

Study population

This was a cross-sectional study of non blood-related subjects from Nanchong of Sichuan province. The participants (at least 18 years of age) were consenting individuals undergoing coronary angiography at the Central Hospital of Nanchong in 2011-2014. The indications for angiography included exercise-induced chest pain, previously diagnosed myocardial infarction, and atypical chest pain. Coronary angiograms were obtained using standard techniques and multiple views were recorded. Patients with > 50% stenosis in one or more arteries were included in the case group, while those with a maximum stenosis of < 10% in any artery were included in the control group. Major exclusion criteria were history of coagulation disorders, familial hypercholesterolemia, New York Heart Association Class III and Class IV heart failure, ongoing systemic inflammatory diseases, renal or hepatic dysfunction, significant val-

Table 3. Hardy-Weinberg equilibrium test for control group

SNP	Measured value (Predicted value)			Hardy-Weinberg equilibrium	
	1/1	1/2	2/2	x^2 value	*P* value
GPIaC807T	77 (78.4)	65 (62.3)	11 (12.4)	0.295	0.587
GPIbαKOZAK-5T/C	97 (94.1)	46 (51.8)	10 (7.1)	1.897	0.168
GPVIT13254/C	153 (153.0)	0 (0.0)	0 (0.0)	0.000	1.000
HPA-1	152 (152.0)	1 (1.0)	0 (0.0)	0.002	0.968
HPA-2	142 (142.2)	11 (10.6)	0 (0.2)	0.213	0.645

1/1 = homozygous wild-type, 1/2 = heterozygotes, 2/2 = mutant homozygotes, the polymorphisms were consistent with Hardy-Weinberg equilibrium in the control group (P > 0.05).

Table 4. Genotype and allele frequency distributions of platelet membrane glycoprotein polymorphisms

Genotype and Allele	Case (n=150*) n (%)	Control (n=153) n (%)	x^2 value	*P* value
GPIaC807T			6.640	0.036
CC	61 (40.9)	77 (50.3)		
CT	64 (43.0)	65 (42.5)		
TT	24 (16.1)	11 (7.2)		
			5.725	0.017
C	186 (62.4)	219 (71.6)		
T	112 (37.6)	87 (28.4)		
GPIbαKOZAK-5T/C			2.450	0.294
TT	82 (54.7)	97 (63.4)		
TC	57 (38.0)	46 (30.1)		
CC	11 (7.3)	10 (6.5)		
			1.889	0.169
T	221 (73.7)	240 (78.4)		
C	79 (26.3)	66 (21.6)		
GPVIT13254/C			**	0.059
TT	146 (97.3)	153 (100.0)		
TC	4 (1.3)	0 (0.0)		
			**	0.004
T	296 (97.4)	306 (100.0)		
C	8 (2.6)	0 (0.0)		
HPA-1			**	1.000
TT	149 (99.3)	152 (99.4)		
TC	1 (0.7)	1 (0.6)		
			**	1.000
T	299 (99.7)	305 (99.7)		
C	1 (0.3)	1 (0.3)		
HPA-2			0.002	0.962
CC	139 (92.7)	142 (92.8)		
CT	11 (7.3)	11 (7.2)		
			0.002	0.962
C	289 (96.3)	295 (96.4)		
T	11 (3.7)	11 (3.6)		

*One SNP genotype data was lacking in GPIaC807T. x^2-test was performed to compare the genotypes and alleles between the two groups. **Fisher's exact test.

vular disease, myocarditis, cardiomyopathies, malignancy, or non-consenting patients. This study was approved by the ethics committee of the North Sichuan Medical College, Nanchong, China. Written informed consent was obtained from every participant before data collection.

Data collection procedures

The demographic characteristics of the participants were recorded. Baseline data was ascertained by trained research staff according to the standard operating procedures. Venous blood was drawn from the forearm of each participant under fasting condition. FBG, TG, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), C-reactive protein (CRP) and homocysteine (HCY) levels were measured using the Hitachi 7020 automatic analyzer (Hitachi, Tokyo, Japan). Polymorphisms of platelet membrane glycoproteins GPIaC807T (rs1126643), GPIbαKOZAK-5T/C (rs2243093), GPVIT13254/C (rs1613662), HPA-1a/b (rs5918) and HPA-2a/b (rs6065) were detected by an ABI 3730XL sequence detection system using the GeneMapper 4.1 (Applied Biosystems, USA) (**Table 1**).

Statistical analysis

A total of 303 subjects were divided into the case group and control group. Data were reported as means ± SD, counts or percentages. x^2-test or Student's t-test was performed to compare the genotypes and means between the two groups. Statistical analyses for multiple group data measurements were

Table 5. Relationship between GPIaC807T, GPIbαKOZAK-5T/C polymorphisms and CHD in different genetic analysis models

Gene analysis model	Group	GPIaC807T			GPIbαKOZAK-5T/C		
		Exposed (%)	Unexposed (%)	OR (95% CI)	Exposed (%)	Unexposed (%)	OR (95% CI)
Additive model	Control	11 (12.5)	77 (87.5)	1.00	10 (9.4)	97 (90.6)	1.00
	Case	24 (28.2)	61 (71.8)	2.75 (1.18-6.71)	11 (11.8)	82 (88.2)	1.30 (0.47-3.60)
Recessive model	Control	11 (7.2)	142 (92.8)	1.00	10 (6.5)	143 (93.5)	1.00
	Case	24 (16.1)	125 (83.9)	2.48 (1.11-5.83)	11 (7.3)	139 (92.7)	1.13 (0.42-3.07)
Dominant model	Control	76 (49.7)	77 (50.3)	1.00	56 (36.6)	97 (63.4)	1.00
	Case	88 (59.1)	61 (40.9)	1.46 (0.90-2.36)	68 (45.3)	82 (54.7)	1.44 (0.88-2.34)
Codominant model	Control	65 (42.5)	88 (57.5)	1.00	46 (30.1)	107 (69.9)	1.00
	Case	64 (43.0)	85 (57.0)	1.02 (0.63-1.65)	57 (38.0)	93 (62.0)	1.43 (0.86-2.37)
Allele model	Control	87 (28.4)	219 (71.6)	1.00	66 (21.6)	240 (78.4)	1.00
	Case	112 (37.6)	186 (62.4)	1.52 (1.06-2.17)	79 (26.3)	221 (73.7)	1.30 (0.88-1.93)

performed using one-way analysis of variance (ANOVA), and least significant difference (LSD) test was subsequently used to compare any two means when there were significant differences among multiple groups. $P < 0.05$ was considered to be statistically significant. Hardy-Weinberg equilibrium was tested using x^2-test to judge the reliability of the gene frequency. Logistic regression analysis was performed to screen for CHD risk factors, predict the occurrence of CHD, and reveal the association of gene polymorphism with CHD. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the significance of differences in relative risk. All data were entered twice and then exported to tab-delimited text files. All analyses were performed with Stata 12.0 software (StataCorp, USA).

Results

Characteristics of study population

A total of 303 subjects (182 men and 121 women) were enrolled in this study. The mean age of the case group was 64.9±10.0 years, and the control group was 65.7±9.4 years. Population characteristics, and the incidence rates of smoking, family history of CHD, diabetes and hypertension in the case and control groups are summarized in **Table 2**. Male gender and smoking were significantly associated with CHD. Age, family history of CHD, diabetes, hypertension, body mass index (BMI), TC and HCY were similar in the two groups ($P > 0.05$). TG, FBG, Fib and ApoB levels were significantly higher in the case group than in the control group ($P < 0.05$). In contrast, LDL and ApoA I levels were lower in the case group than in the control group ($P < 0.05$).

Distributions of genotype and allele frequency

The five SNP loci of the control group were in accordance with Hardy-Weinberg equilibrium (**Table 3**). Except for GPIaC807T and GPIbαKOZAK-5T/C, mutant homozygotes were not found in GPVIT13254/C, HPA-1a/b and HPA-2a/b. GPVIT13254/C were all homozygous wild-type in the control group, with only four heterozygotes in the case group. HPA-1a/b had only one heterozygote each in the two groups. Overall, differences in genotype and allele frequency distributions of GPIaC807T were statistically significant in the two groups (P=0.036). Allele frequency distributions but not genotype distributions of GPVIT13254/C were statistically significant in the two groups (P=0.004). There were no significant differences in the genotype and allele frequency distributions of GPIbα-KOZAK-5T/C, HPA-1a/b and HPA-2a/b in the two groups (**Table 4**).

Genetic analysis models and CHD

Since no mutant homozygotes were found in GPVIT13254/C, HPA-1a/b and HPA-2a/b in the two groups, we only examined the association of GPIaC807T and GPIbαKOZAK-5T/C with CHD in multiple genetic analysis models. The association between GPIaC807T and CHD showed statistically significant differences in the additive model (OR=2.75, 95% CI: 1.18-6.71), followed by the recessive model (OR=2.48, 95%

Table 6. Logistic regression analysis for number of mutant alleles with CHD

No. of mutant alleles	OR (95% CI)	*P* value
0	1.00	
1	1.14 (0.64-2.03)	0.659
2	1.66 (0.88-3.13)	0.116
3	2.51 (1.10-5.75)	0.029
4	4.11 (0.41-41.23)	0.299

Table 7. Stepwise logistic regression analysis for risk factors of CHD

Variables	OR (95% CI)	*P* value
Gender	2.91 (1.44-5.87)	0.003
Smoking	2.59 (1.71-3.92)	0.002
FBG	1.13 (1.01-1.26)	0.037
TG	1.41 (1.00-1.99)	0.049
Fib	1.74 (1.23-2.46)	0.002
GPIaC807T TT genotype	4.00 (1.24-12.88)	0.020*

FBG = fasting blood glucose, TG = triglyceride, Fib = fibrinogen. *Adjusted for gender, smoking, FBG, TG and Fib in order to avoid multicollinearity of unadjusted lipoprotein parameters associated with TG.

CI: 1.11-5.83) and the allele model (OR=1.52, 95% CI: 1.06-2.17), but no association in the dominant and codominant models. Additionally, we found no significant correlation between GPIbαKOZAK-5T/C and CHD in all genetic analysis models (**Table 5**).

Mutant alleles and CHD

Given that a single SNP mutation may not significantly increase the risk of CHD, we counted the number of mutant alleles and explored its association with the risk of CHD. Logistic regression analysis showed that the proportion of CHD patients with different mutant alleles gradually increased with increase in numbers of mutant alleles. The risk of CHD in three mutant alleles carrier was 2.51 times higher than in no mutant allele carrier (P=0.029) (**Table 6**).

Multiple logistic regression analysis

The significantly different parameters from clinical characteristics, blood biochemistry and polymorphisms of platelet membrane glycoprotein were included in the multiple logistic regression analysis. In order to avoid the regression equation of multicollinearity, we eliminated TC, LDL, HDL, ApoA I and ApoB that were associated with TG. The TT genotype of GPIaC807T was an independent risk factor of CHD after adjusting for gender, smoking, FBG, TG and Fib (OR=4.00, P=0.020, 95% CI: 1.24-12.88) (**Table 7**).

Discussion

Many studies explored the correlation between polymorphisms of platelet membrane glycoprotein and CHD, but the results were inconsistent. One of the most important reasons is the minor effect of a single gene mutation on CHD. So it is feasible and necessary to combine the detection of multiple gene loci for studying the genetic association with CHD.

Numerous investigations suggested that GPIaC807T, GPIbαKOZAK-5T/C, HPA-1a/b, HPA-2a/b and GPVIT13254C were associated with CHD [6, 12-15]. However, most evidences were completely contradictory [16-19]. Our study found that the HPA-1a/b gene polymorphism was very rare in Chinese population, which was consistent with the findings of another report [20]. There was no association between GPIaC807T polymorphisms and myocardial infarction or CHD in Japanese and Iranians [18, 21]. However, we confirmed that the polymorphism of GPIaC807T had a strong association with CHD in Chinese, which was consistent with the findings of previous studies [22, 23], suggesting that race was an important factor in the distributions of genes.

Two studies from China detected polymorphisms of multiple SNP loci associated with CHD, but no relationship between the numbers of mutant alleles and the risk of CHD [13, 24]. We found that the risk of CHD increased with the increase in numbers of mutant alleles. When mutant alleles were individually examined, they showed no effect on CHD. However, when treated as a whole, they were associated with the risk of CHD.

Due to the limitations of objective conditions, our sample size was small. The mutant alleles frequencies of HPA-1a/b, HPA-2a/b and GPVIT-13254C were low in the case group (0.3%, 3.7% and 2.6%, respectively). We found no association between polymorphism of HPA-1a/b and CHD, and HPA-1a/b had no homozygous mutant in the two groups. Notably, the

frequency of HPA-1a/b mutation was only 0.3%, which was consistent with previous studies [20, 25]. We also found no relationship between polymorphism of HPA-2a/b and CHD. Therefore, given the small sample size of our study, although no association was found between the three genes and CHD, they could have a micro effect on CHD.

There may be some confounding factors in our study. Although there was no difference in age distribution, the proportion of males in the case group (77.3%) was higher than in the control group (43.1%). Half of the participants had a history of smoking and 97.2% were males. But, these were consistent with the current epidemiology of CHD in China [26]. We did not exclude patients with old myocardial infarctions and previous diagnosis of CHD, even though they had already modified their diets or undergone effective lipids-modulating therapy. Therefore, we found lower levels of TC and LDL in the case group as compared to the control group, rather than the expected higher levels.

Conclusion

We confirmed that the GPIaC807T polymorphism had a strong association with CHD in China, and the TT genotype was an independent risk factor of CHD. The C allele of GPVIT13254/C may increase the risk of CHD. There were no correlations of GPIbαKOZAK-5T/C, HPA-1a/b and HPA-2a/b polymorphisms with CHD. We found that the risk of CHD was positively correlated with the numbers of mutant alleles, whereby the more the numbers of mutant alleles, the higher was the risk of CHD. We believe that combined detection of multiple gene SNP loci should be the focus of future genetic association studies of CHD.

Acknowledgements

This work was supported by Department of Cardiology, Central Hospital of Nanchong, China.

Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: TL JDH WN HL. Performed the experiments: JDH WN. Analyzed the data: JDH WN HL. Contributed reagents/materials/analysis tools: WN JDH HL. Wrote the paper: WN.

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