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*Original Article*

# Association between polymorphisms of platelet membrane glycoprotein Ibα and risk of coronary heart disease in Han Chinese, Henan, China

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**Abstract:** Objective: To study the relationship between human platelet alloantigens-2 (HPA-2) polymorphism, Kozak sequence polymorphism, macroglycopeptide region variable number of tandem repeats (VNTR) polymorphism of GPIbα and coronary heart disease (CHD). Methods: In the present study, blood obtained from 403 patients with CHD and 500 healthy controls was detected by PCR or PCR-RFLP methods to analyze the genotypes of HPA-2, Kozak sequence and VNTR. Results: About HPA-2 polymorphism, there were significant differences between CHD group and control group in TM+MM genotype (13.15% vs. 8.60%, $P < 0.05$; OR 1.609; 95% CI 1.051 to 2.463) and M alleles distributions (6.58% vs. 4.40%, $P < 0.05$; OR 1.645; 95% CI 1.090 to 2.482). For Kozak sequence polymorphism, between control group and CHD group, the difference of CC genotype distribution is statistic significance (3.20% vs. 7.69%, $P < 0.05$; OR 2.000; 95% CI 1.076 to 3.718). The genotype analysis of VNTR in Han People of Henan (AC, BC, BD, CC, CD and DD) proved that no association between any genotypes or alleles and CHD. There weren't any significant differences about haplotypes of these genes between control group and CHD group ($P > 0.05$). Conclusions: The M allele of HPA-2 could be an important risk factor for CHD; the CC genotype of Kozak sequence would be a biomarker of genetic susceptibility about CHD; and each genotype of VNTR is no associated with CHD. No significant differences between control group and CHD group about haplotypes of these genes.

**Keywords:** HPA-2, Kozak sequence, VNTR, polymorphism, CHD

## Introduction

Coronary heart disease (CHD), one of the serious cardiovascular diseases (CVDs) which are the leading causes of mortality and morbidity in the world [1, 2], harms human health seriously and causes death. CHD is caused by the plaque built up on the walls of coronary arteries that bring blood and oxygen to human's heart, and this plaque formed by fatty material and other substances can narrow arteries and result in blood flow to the heart slowing down or stopping.

Platelet plays an essential role in thrombosis and homeostasis and holds the integrity of the vascular system. It can rapidly adhere to components of the newly exposed underlying fibrous matrix and form blood clots, then stop bleeding when endothelial cell lining damaged [3]. At the same time, extreme thrombus formation under pathological conditions may result in vessel occlusion [4]. The thrombus of coronary artery formed from the rupture of atherosclerotic plaque is also the physiological basic of CHD. Glycoprotein (GP) Ib-IX-V is a platelet membrane receptor complex, it plays a key role in mediating platelet activity and thrombosis [5].

GP Ib-IX-V complex consists of four different polypeptide chains [6]. GPIbα is the major subunit of the complex and contains all of the known extra cellular ligand-binding sites [7]. So its gene polymorphism may influence the structure and quantity of the receptor complex, which further influence the platelet adhesion, activity and aggregation. There are four poly-

**Table 1.** Genotype distribution and allele frequency of the HPA-2 polymorphism in the study group

| | Genotype | | | Total genotypes | Allele | | Total alleles |
|---|---|---|---|---|---|---|---|
| | TT | TM | MM | | T | M | |
| % Distribution | 89.37 | 10.52 | 0.11 | | 94.63 | 5.37 | |
| n | 807 | 95 | 1 | 903 | 1709 | 97 | 1806 |

**Table 2.** Genotype distribution and allele frequency of the Kozak polymorphism in the study group

| | Genotype | | | Total genotypes | Allele | | Total alleles |
|---|---|---|---|---|---|---|---|
| | TT | TC | CC | | T | C | |
| % Distribution | 60.69 | 34.11 | 5.20 | | 77.74 | 22.26 | |
| n | 548 | 308 | 47 | 903 | 1404 | 402 | 1806 |

morphisms associated with GPIbα, first, the human platelet antigen-2 (HPA-2) system, characterized by a C/T transition at nucleotide 1018 and result that an amino acid dimorphism (Thr/Met) at residue 145 [8]; second, the Kozak sequence contains a single nucleotide substitution (T/C) [9]; the third one is associated with variations in the number of 13 amino acid tandem repeats (VNTR) in the macroglycopeptide region [10]. The VNTR consists of four variants: A, B, C, D(in order of decreasing molecular mass and means 4 repeats, 3 repeats, 2 repeats and 1repeat respectively) [11]. And the fourth one, a TaqI polymorphism in the 3' untranslated region [12]. So we forecasted that the former three gene polymorphisms would be associated with platelet adhesion, activity and aggregation.

By now, the association between the GPIbα polymorphism and CHD is controversial and only a few large-scale studies had been done. So it will be of epoch-making significance if we study the pathogenesis of CHD from the genetic aspect.

## Materials and methods

*Selection of patients and control subjects*

The study protocol was approved by the Ethical Committee of bioscience, Zhengzhou University, China, and written informed consent was obtained from all patients before study entry. We considered 403 cases of patients with CHD hospitalized in the department of cardiovascular medicine (including male cases and female cases aged between 36 and 64 years old), they were diagnosed as myocardial infarction (MI) (242 patients) and unstable angina (UAP) (161 patients) by an electrocardiogram, blood tests or a coronary angiogram before clinical procedures or drug therapy such as antiplatelet drugs. And 500 healthy controls diagnosed without clinical history or family history of CHD and with normal coronary arteries were recruited by random sampling in the same age range. These subjects were investigated by case-contro1 studies and are all Han People in Henan district.

*DNA genotyping*

Blood samples were obtained from peripheral blood and stored in 1% EDTA-$Na_2$ at -80°C. Total genomic DNA was extracted from the buffy coat of blood samples lysed in sodium dodecyl sulfate (SDS) and proteinase K, and then purified DNA by phenol/chloroform and ethanol precipitation. The DNA sequence spanning the polymorphisms of GPIbα HPA-2, Kozak sequence and VNTR were amplified by polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP). The reaction system contained genomic DNA, TaqPCR MasterMix (TAKARA), forward and reverse oligonucleotide primers, and were performed in an Eppendorf cycler. Gel electrophoresis of all products was carried out on 2% agarose gel stained with EB subsequently.

The sequence of HPA-2 forward primer is 5'-GGA CGT CTC CTT CAA CCG GCT-3', and the reverse primer sequence is 5'-GCT TTG GTG GGG AAC TTG AC-3'. PCR assay: 94°C for 5 min followed by 35 cycles of 94°C for 1 min, 60°C for 1 min, and 72°C for 2 min; and a final extension step of 7 min at 72°C. After amplification, the PCR product was digested with restriction enzyme AcyI at 37°C for 16 hours.

For the Kozak sequence polymorphism , the forward primer sequence is 5'-AGG TCT TTC TGC CTG CCT GT-3', and the reverse sequence is 5'-TAG CCA GAC TGA GCT TCT CC-3'. The cycling parameters were 94°C for 10 min fol-

**Table 3.** Genotype distribution and allele frequency of the VNTR polymorphism in the study group

| | Genotype | | | | | | Total genotypes | Allele | | | | Total alleles |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AC | BC | BD | CC | CD | DD | | A | B | C | D | |
| % Distribution | 0.78 | 0.66 | 1.66 | 40.42 | 36.21 | 20.27 | | 0.39 | 1.16 | 59.25 | 39.20 | |
| n | 7 | 6 | 15 | 365 | 327 | 183 | 903 | 7 | 21 | 1070 | 708 | 1806 |

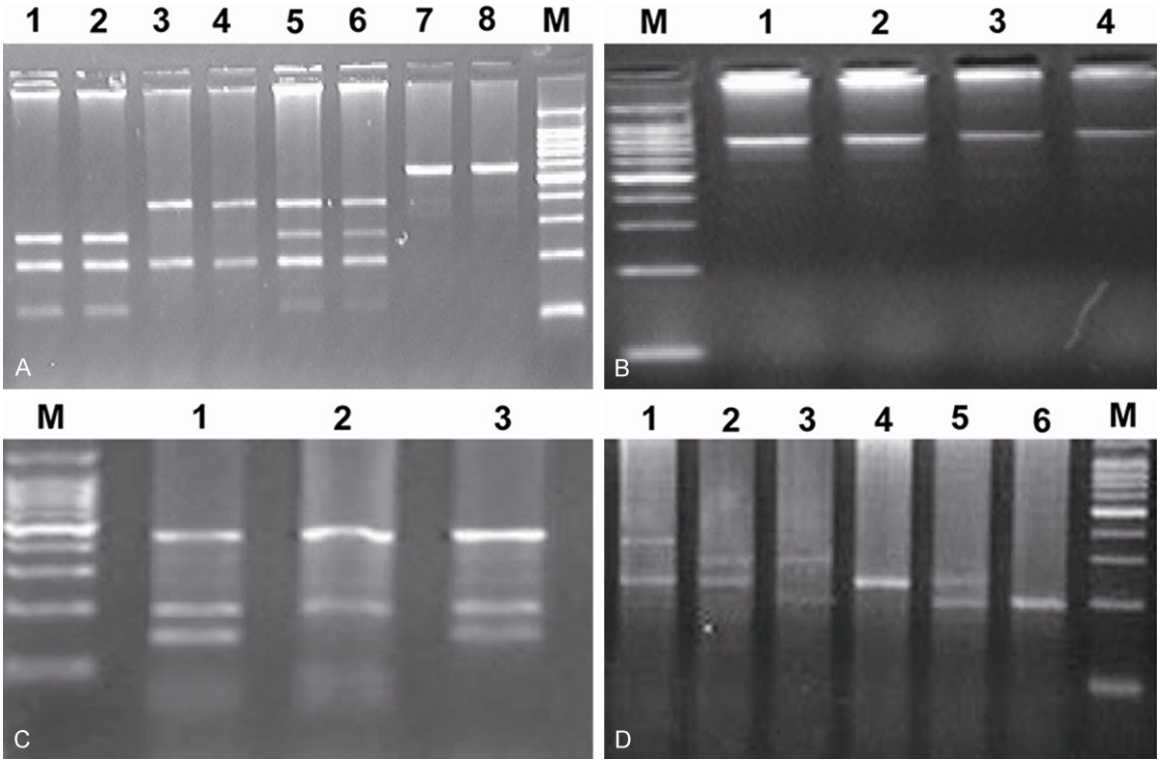


**Figure 1.** Amplification of HPA-2, Kozak and VNTR sequences from total genomic DNA of blood samples by polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP). A. Amplification of HPA-2 sequence by PCR/RFLP; TT homozygote (270 bp, 201 bp, 120 bp) (lanes 1, 2), TM heterozygote (390 bp, 270 bp, 201 bp, 120 bp) (lanes 5, 6), MM homozygote (390 bp, 201 bp) (lane 3, 4), HPA-2 PCR products (lanes 7, 8) and 100 bp DNA Marker (lane M). B. Amplification of Kozak sequence (774 bp) by PCR (lanes 1, 2, 3, 4) and 100 bp DNA Marker (lane M). C. Amplification of Kozak sequence by RFLP; CC homozygote (441 bp, 192 bp, 81 bp, 60 bp) (lane 2), CT heterozygote (441 bp, 192 bp, 141 bp, 81 bp, 60 bp) (lane 1), TT homozygote (441 bp, 192 bp, 141 bp) (lane 3) and 100 bp DNA marker (lane M). D. Amplification of VNTR sequence by PCR/RFLP; four variants: A (312 bp), B (273 bp), C (234 bp), D (195 bp) in six genotypes AC (lane 1), BC (lane 2), BD (lane 3), CC (lane 4), CD (lane 5), DD (lane 6), 100 bp DNA Marker (lane M).

lowed by 5 cycles of 94°C for 1 min, 65°C for 1 min, and 74°C for 2 min; then followed by 30 cycles of 94°C for 1 min, 60°C for 2 min, and 74°C for 2 min; a final extension step of 7 min at 72°C. Then the PCR product was digested with restriction enzyme Hae III at 37°C for 3 hours.

The forward primer of the VNTR polymorphism is 5'-CAC TAC TGA ACC AAC CCC AAG-3', and the reverse primer sequence is 5'-TTG TGG CAG ACA CCA GGA TGG-3'. DNA amplifications were performed under the following conditions: 94°C for 5 min followed by 50 cycles of 94°C for 1 min, 62°C for 1 min, and 72°C for 1 min; a final extension step of 7 min at 72°C.

*Statistical analysis*

All variables were analyzed by the $X^2$ test or Fisher's exact test. A $P$ value ≤ 05 was considered as statistical significant. The strength of association between the gene polymorphisms and the occurrence of CHD was estimated by the odds ratio (OR) with its 95% confidence intervals (CIs). The SHEsis online software [13]

**Table 4.** Genotype distribution and allele frequency of the HPA-2 polymorphism between the CHD group and the control group

| | Genotype | | | Allele | |
|---|---|---|---|---|---|
| | TT | TM* | MM* | T | M* |
| CHD group | 350 (86.85) | 53 (13.15) | 0 (0.00) | 753 (93.42) | 53 (6.58) |
| Control group | 457 (91.40) | 42 (8.40) | 1 (0.20) | 956 (95.60) | 44 (4.40) |

Values are n (%). *There were significant differences of TM+MM genotype distributions between control group and CHD group (P < 0.05, OR 1.609, 95% CI 1.051 to 2.463). *In control group and CHD group, the distribution of M allele reached statistics significance (P < 0.05, OR 1.645, 95%CI 1.090 to 2.482).

were used to perform haplotype analysis of these three genes.

## Results

Genotype frequency and haplotype analysis (**Tables 1-3**) confirmed that HPA-2 polymorphism, Kozak polymorphism and VNTRpolymorphism were in Hardy-Weinberg equilibrium in the study population.

PCR products of the HPA-2 polymorphism was 591-base pair (bp), after digest by AcyI, it could products three genotypes: TT homozygote (270 bp, 201 bp, 120 bp), TM heterozygote (390 bp, 270 bp, 201 bp, 120 bp), MM homozygote (390 bp, 201 bp) (**Figure 1A**). Analysis of the HPA-2 genotype frequency and haplotype detected that a significant differences between the two groups with regard to frequences of T/M+M/M genotype n (%): 43 (8.60%) in control group *v* 53 (13.15%) in CHD group, showed there were an association between TM+MM genotype and CHD ($P < 0.05$; OR 1.609; 95% CI 1.051 to 2.463); the distribution of M allele were 4.40% in control group and 6.58% in CHD group reached statistics significance suggested the risk of CHD has an association with allele frequency ($P < 0.05$; OR 1.645; 95% CI 1.090 to 2.482) (**Table 4**).

PCR products of the Kozak sequence site was 774 bp (**Figure 1B**), after digest by Hae III, it could products three genotypes: CC homozygote (441 bp, 192 bp, 81 bp, 60 bp), CT heterozygote (441 bp, 192 bp, 141 bp, 81 bp, 60 bp), TT homozygote (441 bp, 192 bp, 141 bp), showed in **Figure 1C**. The Kozak genotype frequency and haplotype analysis confirmed that there were significant difference of CC genotype distribution between control group and CHD group (3.20% *vs.* 7.69%), pointed there was an association between CHD and CC ($P < 0.05$; OR 2.000; 95% CI 1.076 to 3.718); in control group and CHD group, the distribution of C allele were 23.4% and 26.7%, respectively, which didn't reach statistics significance ($P > 0.05$) (**Table 5**).

The polymorphism was shown to result from a variable number of tandem repeats (VNTR) of 39 bp in the macroglycopeptide region of GPIb, contains 6 genotypes: AC, BC, BD, CC, CD, DD, and the PCR products were 195 bp, 234 bp, 273 bp, 312 bp (**Figure 1D**). Analysis of the association of the VNTR polymorphism with CHD showed there weren't significant differences of the 6 genotypes distributions between control group and CHD group ($P > 0.05$, respectively) (**Table 6**).

The SHEsis online software was used to perform Haplotype analysis of the HPA-2, Kozak sequence and VNTR polymorphisms. All those allele frequency < 0.03 was ignored in analysis. There weren't any significant differences of haplotypes of these three between control group and CHD group ($P > 0.05$, respectively) (**Table 7**).

## Discussion

CHD is one kind of complex disease induced by a variety of well determined risk factors. The most common risk factors include hypertension, hyperlipidemia, obesity [14], family history, smoking, diabetes, stress and lack of exercise and the like [15]. Recently years, more and more evidences showed that the prevalence of CHD should be attributed to the interactions of genetic susceptibility, long-lasting environmental influence and undercurrent disorders [16].

In a coronary artery branch which has arterial thrombosis, there is underlying atheromatous plaque rich of platelet in the epicardial segment [17]. And the platelet adhesion and aggregation are critical elements in the coronary thrombosis [18], the platelet membrane receptor complex GPIb-IX-V mediate platelet adhesion to von Willebrand factor (vWF) bound to the subendothelium under high shear stress conditions. Alternatively, pathological shear stress in an occluded artery can initiate aIIbh3-dependent

**Table 5.** Genotype distribution and allele frequency of the Kozak polymorphism between the CHD group and the control group

| | Genotype | | | Allele | |
|---|---|---|---|---|---|
| | CC* | CT | TT | C | T |
| CHD group | 31 (7.69) | 153 (37.97) | 219 (54.34) | 215 (26.67) | 591 (73.33) |
| Control group | 16 (3.20) | 155 (31.00) | 329 (65.80) | 187 (18.70) | 813 (81.30) |

Values are n (%). *There were significant differences of CC genotype distribution between control group and CHD group ($P < 0.05$, OR 2.000, 95% CI 1.076 to 3.718) in control group and CHD group, the distribution of C allele didn't reach statistics significance ($P > 0.05$).

**Table 6.** Genotype distribution and allele frequency of the VNTR polymorphism between the CHD group and the control group

| | Genotype | | | | | | Allele | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | AC | BC | BD | CC | CD | DD | A | B | C | D |
| CHD group | 3 (0.74) | 4 (0.99) | 7 (1.73) | 166 (41.19) | 138(34.24) | 85 (21.04) | 3 (0.37) | 11 (1.37) | 477 (59.40) | 315 (39.23) |
| Control group | 4 (0.80) | 2 (0.40) | 8 (1.60) | 200 (40.00) | 188 (37.60) | 98 (19.60) | 4 (0.40) | 10 (1.00) | 594 (59.40) | 392 (39.20) |

Values are n (%). There were no significant differences of the 6 genotypes distributions between control group and CHD group, $P > 0.05$, respectively.

**Table 7.** Haplotype analysis of HPA-2, Kozak sequence and VNTR polymorphism

| Haplotype | Case (freq) | Control (freq) | $x^2$ | *P* | Odds ratio [95% CI] |
|---|---|---|---|---|---|
| T+T+C | 283.78 (0.356) | 288.66 (0.386) | 1.242 | 0.26 | 0.888 [0.720~1.095] |
| T+T+D | 253.38 (0.318) | 248.11 (0.332) | 0.229 | 0.63 | 0.949 [0.765~1.177] |
| T+C+C | 92.89 (0.116) | 85.34 (0.114) | 0.043 | 0.84 | 1.034 [0.755~1.414] |
| T+C+D | 99.95 (0.125) | 76.89 (0.103) | 2.116 | 0.15 | 1.264 [0.921~1.735] |
| M+T+C | 26.16 (0.033) | 16.16 (0.022) | 1.893 | 0.17 | 1.550 [0.826~2.906] |

aggregation through inducing GPIb-IX-V to bind to plasma vWF, and the thrombus from this can block blood supply and cause thrombotic disease [19, 20].

The GPIb-IX-V consists of four different polypeptide chains: GPIbα, GPIbβ, GPIX and GPV. GPIbα chain is the functionally dominant subunit of the receptor complex for binding vWF in its N-terminal domain [21]. The HPA-2 polymorphism is located close to the vWF binding site, could cause a conformational variation in the structure of GPIbα and might affect the ligand binding. Recent studies found an association between HPA-2 and cardiovascular diseases [22]. Kozak sequences is important because surrounding ATG initiator codons, and be associated with increased expression of the GPIb-IX-V complex on the surface of CHO cells in vitro studies [9]. Different variant of VNTR represents different distance between GPIbα and the platelet surface, and the length of GPIbα could affect the efficiency of platelet adhesion for different distance between the VWF binding site and the vessel wall [23]. The VNTR showed strong linkage to the HPA-2 polymorphism, alleles with C or D are linked to the Thr-isoform, alleles with A or B are linked to the Met-isoform [11]. There may be relationship between these three polymorphism and CHD.

Recently years, there were different research outcomes about the association between HPA-2 and CHD because of the different races and samples. In 1996, American scholar first reported there weren't association between HPA-2 and CHD, but contrary outcomes are also existed [24, 25]. Our research showed that there were significant differences of TM+MM genotype and M allele distributions between control group and CHD group, and there was moderate correlation between this genetic polymorphism and CHD.

Meisel et al [26] first found the association between the C allele of Kozak sequence and ischemic complications of percutaneous transluminal coronary intervention (PCI) in white people suffered from acute coronary syndrome (ACS). Douglas et al [23] found TT homozygote was related to myocardial infarction, while the C allele in TC heterozygote was a protect factor

against Our research showed that there were significant differences of CC genotype distributions between control group and CHD group, which indicated moderate correlation between -5T/C Kozak polymorphism and CHD of Chinese people in Henan, China.

Reports about the association between VNTR polymorphism and CHD were distinct. Murata et al [24] found the A allele was independent risk factor for CHD, while Kenny et al [27] and Ito et al [28] reported no relationship between the two. Afshar-Kharghan et al [29] found CC homozygote was related to the low incidence of CHD. Ozelo et al [30] found the frequency of CD genotype in MI of Brazilian was twice than that in control, and more coronary artery was serious stenosis in MI patients with D allele or CD genotype, while there were less serious stenosis of coronary artery in MI patients with C allele or CC genotype . Some other scholars thought BC genotype was related to CHD [25, 31]. The variance of the researches above may due to the different quantity of the samples as well as the genetic heterogeneity. Our research did not get positive outcome about the VNTR polymorphisms and CHD.

CHD is a multi-factors disease. Each factor may have little effect on the development of CHD, and there may exist synergistic or addition effect on CHD among all the factors. One method to determine the genetic interaction states above is Haplotype analysis. Our research couldn't find the relationship between CHD and the 5 haplotypes which appeared frequence > 0.03.

In conclusion, our research suggested that there is a relationship between HPA-2, Kozak sequence polymorphism and CHD, while any haplotype of the three gene polymorphisms do not increase the liability of CHD. But the results still require confirmation by large-scale prospective research, and then may provide more evidence for the development of new antiplatelet drugs, people with the dangerous GPIba gene would most benefit from drug therapy as well.

## Disclosure of conflict of interest

None.

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