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Research Article
Association of Platelet Integrin $\alpha_{IIb}\beta_3$ Polymorphisms with Atherosclerotic Coronary Heart Disease in Sudanese Patients

[1]Lamyaa Ali Elsidege Ali and [2]Fathalrahman Mahdi Hassan

[1]Department of Hematology, College of Post Graduate Studies, University of Science and Technology, Khartoum, Sudan
[2]Department of Clinical Laboratory Science, College of Applied Medical Science, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Abstract

Background and Objective: Glycoprotein IIIa and GPIIb constitutes are the fibrinogen receptor (integrin $\alpha_{IIb}\beta_3$). This glycoprotein has a fundamental role in atherothrombosis. This study aimed to detect the association of $\alpha_{IIb}\beta_3$ polymorphisms with atherosclerotic coronary heart disease in Sudanese patients and the association between the risk factors and platelet integrin $\alpha_{IIb}\beta_3$ polymorphisms. **Materials and Methods:** This is a case-control hospital-based study contain 50 atherosclerotic patients (>18 years) with coronary heart disease that admitted to Khartoum hospital and were compared to apparently 50 healthy Sudanese subjects at the same ages. About 5 mL of venous blood sample was collected from each patient and control. The laboratory analyses were done for HbA1c, lipid profile and for DNA genotyping. **Results:** LDL, HDL, HbA1c and body mass index have shown highly significant influence on patients. No significant differences were observed for triglycerides and total cholesterol levels. The risks of coronary heart disease were higher with A/B genotype in HPA3, but no association detected with coronary heart disease patients in HPA1 polymorphism. **Conclusion:** In conclusion, HPA3 polymorphism was associated with atherosclerotic in Sudanese patients, while HPA1 polymorphism has not.

Key words: Platelet, integrin, $\alpha_{IIb}\beta_3$ polymorphism, coronary heart disease, Sudan

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Corresponding Author: Lamyaa Ali Elsidege Ali, Department of Hematology, College of Post Graduate Studies, University of Science and Technology, Khartoum, Sudan Tel: 00249960414341

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cardiovascular disease (CVD) has been responsible for more deaths than any other disease in the United States[1]. Coronary artery disease (CAD), also known as ischemic heart disease (IHD)[2], refers to a group of diseases, which includes stable angina, unstable angina, myocardial infarction and sudden cardiac death[3]. It is within the group of cardiovascular diseases of which it is the most common type[4]. Risk factors include high blood, smoking, diabetes, lack of exercise, obesity, elevated blood cholesterol, poor diet, depression and excessive alcohol[5,6]. New studies showed the importance of genetic factors in the etiopathologic of Coronary artery disease (CAD)[7]. Understandings of molecular foundation of platelet aggregation localize awareness[8] of $\alpha_{IIb}\beta_3$. Integrin $\alpha_{IIb}\beta_3$ is the most plentiful receptor on the platelet surface and when activated, it joins fibrinogen and VWF[9]. Platelet thrombosis is caused by many platelet membrane receptors including glycoprotein IIb/IIIa[10]. An exchange from thymine (T) to cytosine (C) was present at codon 33 of the GpIIIa, resulting in a Leu33 (PlA1) to Pro (PlA2) change[11]. Human platelet antigen-3 (HPA-3) (Baka/Bakb) is a common polymorphism of platelet GpIIb, resulting from an isoleucine-to-serine substitution from thymine (T) to guanine (G) base change at position 843 of the GpIIb heavy chain[12]. Platelet interaction and cardiovascular disease progression remain an unsolved riddle for many years. It is well identified that platelets have a crucial role in acute coronary syndrome[13]. Giant platelets are adventitial better energetic and constitute a dangerous agent for the development of coronary thrombosis, which induces myocardial infarction[14]. In addition, the platelet- lymphocyte ratio (PLR) has recently emerged as an incoming indicator that can act as a main predictor of inflammatory conditions and gross mortality[15]. An implication of integrin $\alpha_{IIb}\beta_3$ in the pathologic process of coronary artery disease were studied more, but in Sudan, this polymorphism was poorly studied. This study aims to detect the association of $\alpha_{IIb}\beta_3$ polymorphisms with atherosclerotic in Sudanese patients, which has the strength to improve the clinical outcome and reduce the risk of coronary heart disease by identifying the subjects at high risk early.

MATERIALS AND METHODS

This is a case-control hospital-based study contain 50 atherosclerotic patients with coronary heart disease that admitted to Khartoum hospital and were compared to apparently 50 healthy Sudanese subjects at the same ages. All control subjects with hypertension, diabetes mellitus, dyslipidemia or other known risk factors for the disease were excluded from the study. The ages of study population were more than 18 years. Questionnaires were filled from patients and control that included age, sex, weight, height, smoking and blood pressure. The study protocol was reviewed and approved by the Deanship of Scientific Research Ethical Committee of the University Science and Technology. An informed oral consent was obtained from all participants after full explanation of the purpose of the study. About 5 mL of venous blood sample was collected from each patient and control into two containers 2.5 mL in EDTA to assess (HbA1c, DNA genotyping), 2.5 mL in lithium heparin for lipid profile. The laboratory analyses were done for HbA1c used Clover A1cTM self-analyzer, for lipid profile used Vitros 250 machines and for DNA genotyping used PCR and RFLP. Genomic DNA was extracted by Qiagen DNA protocol and stored at -20°C.

Polymerase chain reaction (PCR): Oligonucleotide primers selected for the polymerase chain reaction (PCR) were used to amplify those parts of the genomic DNA that contain the polymorphic sequences corresponding to the HPA-1 and HPA-3 alleles. The HPA-3 polymorphism was identified by PCR amplification of a 253 bp fragment with use of the forward primer (5 -CTC AAG GTA AGA GCT GGG TGG AAG AAA GAC-3), the reverse primer (5-CTC ACT ACG AGA ACG GGA TCC TGA AGC CTC-3). The HPA-1 polymorphism was discovered by PCR amplification of a 338 bp fragment with use of the forward primer (5-CTG CAG GAG GTA GAG AGT CGC CAT AG-3), the reverse primer (5-CTC CTC AGA CCT CCA CCT TGT GCT CT -3)[16]. PCR reaction mixture 20 µL was prepared by adding 5 µL of DNA template, 1 µL from each forward and reverse primer and 13 µL of DW with master mix[16] (Maxime PCR Premix kit (i-*Taq*). For GpIIb, 28 cycles of PCR were run at 94°C for 5 min, 94°C for 45 sec, 63°C for 45 sec, 72°C for 1 min and 72°C for 7 min; for GpIIIa, 30 cycles of PCR were run at 95°C for 5 min, 95°C for 45 sec, 62°C for 45 sec, 72°C, for 1 min and 72°C for 5 min[16]. The PCR products for both genes were hold at 4°C. The PCR products were analyzed by used 1.5 agarose gel with 10 µL of ethidium bromide. About 10 µL PCR products and 5 µL DNA ladder size marker 100 pb (Intron-Korea) were run in electrophoresis machine for 45 min. DNA bands 253 pb for GpIIb and 338 pb for GpIIIa were visualized and detected by using high the high-performance ultra-violet documentation system.

Restriction-enzyme digestion: The PCR products were digested by using restriction enzyme Fok I (Cut Smart-NEB) for determination of HPA3 and ScrFI (cut smart NEB) for

determination of HPA1. The total of 20 µL of enzymes mixture prepared by adding 0.4 µL Of FoK1, 2 µL buffer, 10 µL PCR product, 7.6 µL (H_2O) and 1 µL of ScrF1, 2 µL Buffer, 10 µL PCR product, 7 µL H_2O. These mixtures were incubated in 37°C for 16 h over night and inactivated of enzyme reaction by 65°C for 20 min, then 4°C holding temperature. About 10 µL of the digested DNA fragments with 5 µL of DNA ladder were run out in to 2% agarose gel containing ethidium bromide and the result reading against DNA ladder 100 pb and identified under high performance ultra violet transilluminator gel documentation system. For HPA-3, the presence of Ile at position 843 caused a cleavage of the 253 bp fragment into a 126 and 127 bp fragment, while the presence of Ser was identified by the uncleaved 253 bp fragment. Genotypes were classified as AA (Ile, Ile), AB (Ile, Ser) and BB (Ser, Ser). For HPA-1, the presence of Leu at position 33 caused the cleavage of the 338 bp fragment into a 214, 46 and 78 bp fragment, respectively, whereas the presence of pro-resulted in the cleavage of the 338 bp fragment into 77, 137, 46 and 78 bp fragment, respectively. Genotypes were classified as AA(Leu, Leu), AB (Leu, Pro) and BB (Pro, Pro)[16,17].

Data analysis: Statistical analyses were conducted using SPSS (version 20; SPSS Inc., Chicago, IL) software. Data were expressed as percentage. Descriptive analyses of percentages of categorical variables were reported using Chi's square x2. Comparisons of continuous variables made using the Student's t-test for parametric data. It constructed a logistic regression model to estimate odds ratios and their 95% confidence intervals for the association between genotypes and risk of atherosclerotic coronary heart disease. The Hardy-weinberg Equilibrium was tested to compare genotypes and allele's frequencies among patients and controls. An alpha value of <0.05 denoted a statistically significant difference in all comparisons.

RESULTS

The study population was 50 atherosclerotic patients met the eligibility criteria and 50 controls group. Compared with controls group, LDL, HDL, HbA1c and body mass index were shown highly significant influence on patients (p<0.05). Neither TRI.G nor CHOL increased the risk of coronary heart (p-value more than 0.05) as shown in Table 1. The patients were comprised of 60% males and 40% females with the control groups as shown in Table 2. There were highly significant differences in the frequencies of current smoking and hypertension (56 and 34%, respectively) (p<0.001). Furthermore, three main genotypes of HPA3 were identified in the patients and controls as shown in Table 3. The genotype

Table 1: Distribution of lipid profile and HbA1c among atherosclerotic coronary heart patients and control

	Mean±SD		
Characteristics	Coronary heart patients (n = 50)	Control (n = 50)	p-value
TRI.G (mg dL^{-1})	95.10±60.75	81.32±18.39	0.138
CHOL (mg dL^{-1})	148.16±47.79	132.00±35.23	0.059
LDL (mg dL^{-1})	91.82±35.82	74.46±29.02	0.009*
HDL (mg dL^{-1})	41.14±21.51	55.00±11.25	0.000**
HbA1c (%)	6.39±2.07	4.66±0.83	0.000**
BMI	30.95±7.16	22.94±4.59	0.000**

*p<0.05 statistical significant, **p<0.001 highly statistical significant

Table 2: Risk factors associated with atherosclerotic coronary heart among patients and control

	N (%)		
Characteristics	Coronary heart patients	Control	p-value
Gender			
Male	30 (60.0)	38 (76.0)	0.086
Female	20 (40.0)	12 (24.0)	
Smoking status			
Yes	28 (56.0)	0	0.000*
No	22 (44.0)	50 (100)	
Hypertension			
Yes	33 (66.0)	0	0.000*
No	17 (34.0)	50 (100)	

*p<0.001 highly statistical significant

A/A was the most common genotype in patients (80.0%) and controls (90.0%). Individuals with A/B genotype had 10.13-fold increased risk of developing coronary heart patients compared to those with A/A genotype (OR = 10.13; 95% CI, 1.23-83.47) and this was significant different (p<0.05). Among patients with B/B had 0.28-fold decreased risk developing coronary heart patients compared to those with A/A genotype, but this was not significant different (p>0.05). In patients and controls, three main HPA1 genotypes have been identified as shown in Table 4. Genotyping showed that the frequencies of the A and B alleles were 99 and 1% among patients, respectively, which was in accordance with the Hardy-weinberg equilibrium. This is not statistically significant different from the controls group. Figure 1 showed HPA1 338 pb the human platelet A1 PCR product detected by PCR amplification of a 338 bp fragment using the forward and reverse primers as illustrated. Digestion of the HPA1 PCR product using ScrF1 enzyme was indicated by the 214 pb (leu/leu) genotype of AA as shown in Fig. 2. Figure 3 showed the digestion of the HPA1 PCR product using ScrF1enzyme leading to heterozygotes A/B genotype (214 pb (leu, lue), 137 pb (leu, pro), respectively). Figure 4 showed the digestion of HPA3 PCR product by using of Fok1 enzyme that resulted in the cleavage of the 253 pb fragments into 126 and 127 pb, which were appeared as one lane that shown above in Fig. 4, whereas the presence of serine resulted in un cleavage of 253 pb fragment.

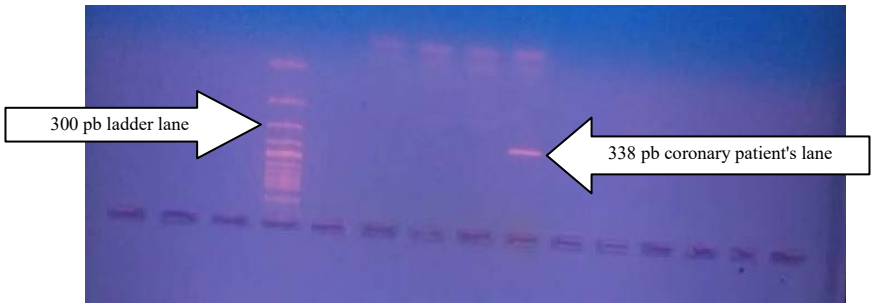

Fig. 1: HPA1 338 pb human platelet A1 PCR product

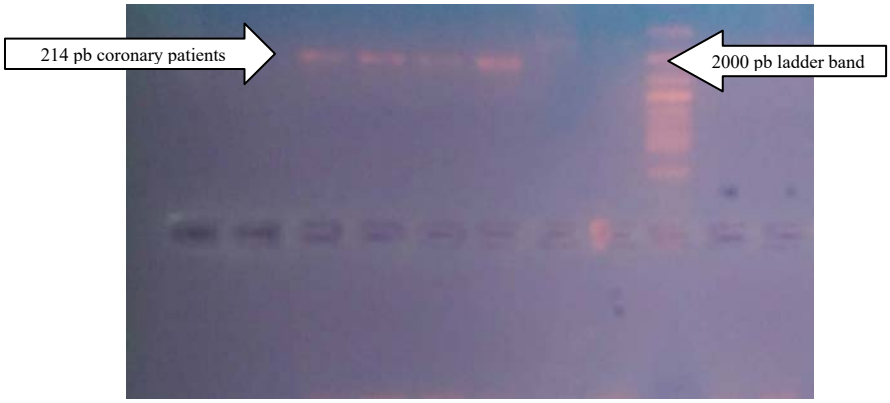

Fig. 2: Enzyme digestion of HPA1 PCR product show homozygous AA genotype 214 Pb (leu, leu)

Table 3: Genotype of HPA3 between coronary heart patient's control

	N (%)			
HPA3	Coronary heart patients	Control	p-value	OR (95% CI)
Normal homozygous A/A	40 (80.0)	45 (90.0)	-	1
Heterozygous A/B	9 (18.0)	1 (2.0)	0.031*	10.13 (1.23-83.47)
Mutant homozygous B/B	1 (2.0)	4 (8.0)	0.265	0.28 (0.03-2.62)
Alleles A	89 (89.0)	91 (91.0)	0.637	1.25 (0.49-3.16)
Alleles B	11 (11.0)	9 (9.0)		

*p<0.05 statistical significant

Table 4: Genotype of HPA1 between coronary heart patient's control

	N (%)			
HPA1	Coronary heart patients	Control	p-value	OR (95% CI)
Normal homozygous A/A	49 (98.0)	50 (100)	0.315	-
Heterozygous A/B	1 (2.0)	0		
Mutant homozygous B/B	-	-		
Alleles A	99 (99.0)	100 (100)	0.316	-
Alleles A	1 (1.0)	0		

p>0.05 not statistical significant

DISCUSSION

Glycoprotein IIIa and GPIIb play a basic role in Atherothrombosis. This glycoprotein is the extremely studied polymorphisms of HPA1 and HPA3, respectively[18]. It constituted the fibrinogen receptor (integrin $\alpha_{IIb}\beta_3$), whose collaboration is considered the last common pathway for platelet aggregation[19]. This study aimed to detect the

association of platelet integrin $\alpha_{IIb}\beta_3$ polymorphisms in Sudanese patients and the association between the risk factors and this polymorphism. Among the studied atherosclerotic patients and control groups, LDL, HDL, HbA1c and body mass index shown most associated with coronary heart disease ($p<0.001$). As expected, there were highly important differences in the frequencies of current smoking and hypertension (56 and 66%, respectively). No statistically relevant differences were observed for triglycerides and total cholesterol levels and this is because all patients were under medications. The present findings were consistent with the suggested risk factors coronary artery disease (CAD)[5,6].

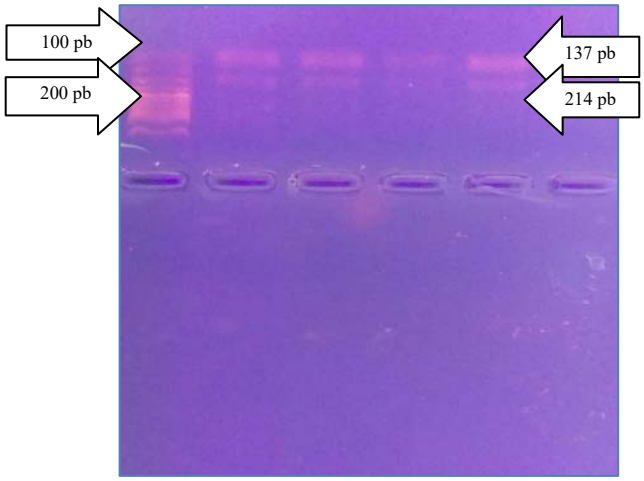

Fig. 3: Enzyme digestion of HPA1 PCR product show heterozygous ab genotype 214 pb normal gene and 137 pb mutant gene (Leu, Pro)

Park *et al.*[20] showed that HPA-3 polymorphism was associated with MI in Korean individuals younger than 56 years of age. This study for HPA3 polymorphism agreed with Park *et al.*[20] and showed that individuals with A/B genotype had 10.13-fold increased risk of developing the disease compared to those with A/A genotype ($p<0.05$). The present study disagreed with Lekakis *et al.*[21] that inspected variations in the frequency of the polymorphism in the GpIIb subunit of the receptor HPA-3 (A and B allele), in patients with more extensive coronary thrombosis and found that there is no association between the HPA-3 genotypes and future cardiovascular events. In this study, Genotype and allele frequencies of HPA1 in coronary heart disease compare to controls were shown that Genotypes A/A was 100% in the control group. On the other hand, patients showed a higher percentage of these genotypes (98%), but these differences were no statistically important ($p>0.05$). Genotyping showed that the frequencies of the A and B alleles were 99 and 1% among patients, respectively, which was in accordance with the Hardy-weinberg equilibrium, this is not statistical relevant different from a controls group ($p>0.05$). The finding agreed with Bottiger *et al.*[22], who concluded that the HPA-1 was not associated with any measurable increase of the risk for CAD or myocardial infarction (MI) in angiographically evaluated subjects[22] and with other studies showed that the PLA1/PLA2 polymorphism did not associate with development of coronary atherosclerosis or the genetic susceptibility to premature MI[23]. The result obtained was disagreed with Weiss *et al.*[18], who reported that the gene frequency of the HPA-1B allele of integrin $\alpha_{IIb}\beta_3$ were higher among junior patients with MI compared with age-matched controls when,

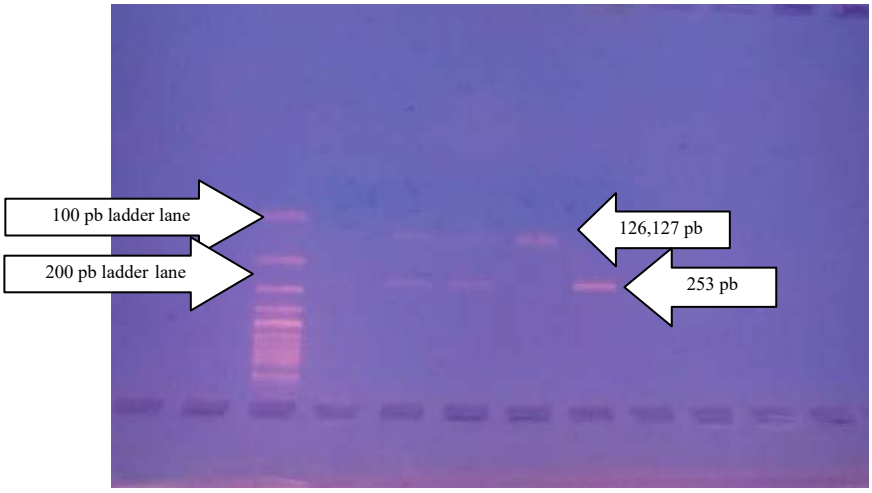

Fig. 4: Enzyme digestion of HPA3 PCR product show heterozygous AB genotype 126 pb, 127 pb normal gene and 253 pb mutant gene (Ile, Ser)

Bojesen *et al.*[24] were assessed the risk of the disease in heterozygotes or homozygotes versus non-carriers. They found that, PlA2/PlA2 homozygosity is associated with a three-fold and four-fold risk of ischemic cardiovascular disease in MI young men. Abu-Amero *et al.*[25] also disagreed with the present study and suggested that the PlA1/PlA1 genotype ($p = 0.029$) was associated with coronary artery disease in Saudi Arabians.

CONCLUSION

Lastly, the finding of the present study indicates that LDL, HDL, HbA1c and body mass index has shown highly significant influence on coronary heart patients. However, no significant differences were observed for triglycerides and total cholesterol levels. The risks of the disease were higher with A/B genotype In HPA3. Genotypes and allele frequencies of HPA1 in coronary heart disease patients and control group showed no difference.

SIGNIFICANCE STATEMENT

This study discovered the association of Integrin $\alpha_{IIb}\beta_3$ polymorphisms with atherosclerotic coronary heart disease in Sudanese patients who can be beneficial for the early identification of subjects at risk in order to prevent the fatal attack of the disease and to help researchers to introduce GpIIb/IIIa antagonist basically in the treatment that many researchers were not able to explore. Thus, a new theory in gene therapy may be arrived at.

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