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Original Article

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Platelet Glycoprotein IIIa *PlA1/PlA2* Polymorphism Modulates the Risk of Myocardial Infarction in Non-Diabetics

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Abstract

Background: Genetic polymorphisms of platelet glycoprotein IIIa (*GPIIIa* gene) have been investigated intensively in several thrombotic diseases, but their role in cardiovascular diseases remains controversial. This study aimed to investigate the association between platelet glycoprotein IIIa *PlA1/PlA2* polymorphism and susceptibility to myocardial infarction in non-diabetics.

Methods: A total of 200 participants were recruited for the study, 100 non-diabetic patients with myocardial infarction and 100 apparently healthy volunteers as a control group. *GPIIIa PlA1/PlA2* polymorphism was analyzed by polymerase chain reaction-restriction fragment length polymorphism.

Results: The distribution of *GPIIIa PlA1/PlA2* polymorphic genotypes among the study groups was significantly different (P value = 0.00). The *PlA1/PlA2* and *PlA2/PlA2* genotypes were more frequent in the patients with myocardial infarction while the genotype *PlA1/PlA1* was more prevalent in the control group. There was a statistically significant association between the *PlA1/PlA1* genotype and reduced risk of both ST-segment elevation myocardial infarction (odds ratio (OR) = 0.19; 95% confidence interval (CI): 0.09 - 0.34, P value = 0.00) and non-ST-segment elevation myocardial infarction (OR = 0.21; 95% CI: 0.09 - 0.45, P value = 0.00). The genotype *PlA1/PlA2* was found to be associated with an increased risk of both types of myocardial infarction (OR = 6.0; 95% CI: 2.61 - 13.8, P value = 0.00 for ST-segment elevation myocardial infarction and OR = 6.65; 95% CI: 2.69 - 16.45, P value = 0.00 for non- ST-segment elevation myocardial infarction. In the patients carrying the *PlA1/PlA2* genotype, the risk of ST-segment elevation myocardial infarction was increased to about 14 folds in the presence of family history (OR: 13.57, 95% CI: 1.42 - 130.03, P value = 0.02), and the risk of non-ST-segment elevation myocardial infarction increased to about 18 folds in the smokers carrying the genotype *PlA2/PlA2* (OR: 17.63, 95% CI: 0.96 - 324.70, P value = 0.05).

Conclusions: The *GPIII PlA1/PlA1* genotype is associated with a reduced risk of ST-segment elevation and non-ST-segment elevation myocardial infarction, while *PlA1/PlA2* is associated with an increased risk of both types of myocardial infarction.

Keywords: Platelet *GPIIIa* polymorphism; ST-segment elevation myocardial infarction; Non-ST-segment elevation myocardial infarction

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Introduction

Myocardial infarction (MI) or heart attack results from a decrease or stoppage of blood supply to a part of the heart, causing the death of cardiac myocytes [1]. According to the result of the electrocardiogram and analysis of cardiac biomarkers, MI is categorized into ST-segment elevation MI (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). STEMI is caused by complete and prolonged blockage of an epicardial coronary artery, and it is defined based on electrocardiogram whereas, NSTEMI arises from partial occlusion or temporary blockage of the coronary artery, or the embolism of microthrombi or atheromatous substances, and it is identified by assessment of cardiac biomarkers [2-6].

Many risk factors for MI are known and categorized into modifiable, such as physical inactivity, smoking, alcohol consumption, diabetes mellitus, hypertension, and obesity, and non-modifiable, such as age, gender, and family history [1-7].

Family history is a significant risk factor for MI. Previously, the genes responsible for the heredity of MI were not well identified. However, with the advancement in molecular genetics methods, several genetic variants associated with the risk of MI have been described [8].

Platelets are small blood cells that play a crucial role in normal hemostatic mechanisms. Once a blood vessel is in-

jured, platelets contribute to the formation of blood clots via adhesion to vascular endothelium, activation, and aggregation; furthermore, activated platelets stimulate the coagulation factors and other mediators to form the fibrin clot and stop the bleeding [9]. Although platelet activation is essential for normal blood clotting, uncontrolled platelet activation can form occlusive thrombi that may cause an ischemic event [10]. The predominant integrin on the surfaces of platelets, known as glycoprotein IIb/IIIa, (GP IIb/IIIa) plays a crucial role in facilitating platelet adhesion, activation, and aggregation [11-13].

The *GPIIIa* gene, situated on chromosome 17, comprises 14 exons with varying lengths spanning from 90 to 3,618 base pairs. A polymorphism known as *PlA1/PlA2* has been detected in the *GPIIIa* gene, leading to the substitution of leucine-33 with proline. This substitution induces a structural alteration in the β3-subunit of the GPIIb-IIIa complex, positioning it extracellularly. As a result, it is biologically plausible to suggest that this polymorphism may have an impact on platelet aggregation and, consequently, on the risk of ischemic cardiovascular disease [14, 15].

Objective

This study aimed to investigate the association between platelet *GPIIIa PlA1/PlA2* genetic polymorphism and susceptibility to MI in non-diabetics.

Materials and Methods

Study design and participants

This is a case-control study in which a convenient sampling method was used to recruit a total of 100 patients presented to the Royal Care International Hospital, Khartoum, Sudan, with clinical features of MI, including chest pain, shortness of breath, fatigue, profuse sweating, nausea, and vomiting. Diagnosis of MI was confirmed based on cardiac troponin, cardiac enzymes, and electrocardiogram. Diabetic patients and patients with cerebrovascular disease, stable and unstable angina, and patients known to have dyslipidemia and any other comorbidity were excluded from the study. In addition, 100 age- and sex-matched healthy volunteers were enrolled as a control group (patient/control ratio = 1:1), and blood samples were collected from them at the same time when the samples were collected from the patients after categorizing the patients into groups based on their age.

Molecular analysis

The *GPIIIa PlA1/PlA2* polymorphism was analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Sample collection, handling, and processing were performed in the same conditions for participants from both study groups.

Blood sample collection and genomic DNA extraction

Blood samples were obtained from all participants, and the DNA was isolated from peripheral white blood cells employing a modified salting-out technique, following the protocol detailed by Sugana et al (2014) [16].

Genotyping of *GPIIIa PlA1/PlA2* polymorphism

A 338 bp fragment of *GPIIIa* gene was amplified in a total volume of 20 µL polymerase chain reaction (PCR) mixture, containing 4 µL master mix (iNtRON Biotechnology, Korea), 2 µL genomic DNA, 1 µL of each of the forward (5'-CTGCAGGAGGTAGAGAGTCGCCATAG-3') and reverse (5'-CTCCTCAGACCTCCACCTTGTGCTCT-3') primers (Macrogen, Korea), and 12 µL distilled water. Thermocycling conditions included an initial denaturation step at 95 °C for 5 min, followed by 37 cycles (denaturation at 94 °C for 30 s, annealing at 65 °C for 30 s, and extension at 72 °C for 30 s), and final extension at 72 °C for 5 min [17].

The amplified fragments were separated on 2% agarose gel and visualized by a gel documentation system (Syengene, Japan).

Restriction digestion

The PCR products were digested with the restriction enzyme "ScrFI" (New England Bio Bas, UK) and separated on 2% agarose gel to determine the genotypic variants of *GPIIIa*. The presence of 214-, 46- and 78-bp fragments was consistent with the *PlA1* allele whereas the presence of 77-, 137-, 46- and 78-bp fragments was consistent with the *PlA2* allele. Based on the size of the fragments, three genotypes were reported (*PlA1/PlA1*, *PlA1/PlA2*, and *PlA2/PlA2*).

Data collection and analyses

Participants' data were collected using a self-administrated questionnaire and from patients' medical records and analyzed using the Statistical Package for Social Sciences (SPSS), version 22. Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as frequency and percentage. The frequencies of different genotypes were calculated, and the difference in genotype distribution among study groups was analyzed by Fisher's exact test. Regression analysis was used to assess the association between the polymorphism and the risk of MI and the interaction between the polymorphic genotypes and conventional MI risk factors. The Hardy-Weinberg equilibrium was calculated to compare the observed genotypic frequencies to the expected ones.

Ethical approval

This study was approved by Al Neelain University's Ethical

Table 1. Distribution of Platelet *GPIIIa PlA1/PlA2* Genotypic Variants Among Study Groups

Study group	*PlA1/PlA1*		*PlA1/PlA2*		*PlA2/PlA2*		P value[a]
	Frequency	%	Frequency	%	Frequency	%	
STEMI	26	43.3%	24	40%	10	16.7%	0.00
NSTEMI	18	45%	17	42.5%	5	12.5%	
Control	80	80%	10	10%	10	10%	

[a]P value is significant at ≤ 0.05. GP: glycoprotein; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.

Review Board, Khartoum, Sudan, and all the methods were performed in compliance with the national guidelines for ethical conduct of research involving human subjects.

Results

Demographic data

A total of 200 participants were recruited for this study; 100 non-diabetic patients with MI were categorized into two groups: 60 (60%) with STEMI and 40 (40%) with NSTEMI; 100 apparently healthy volunteers were enrolled as a control group. The age of MI patients ranged from 25 to 90 years (mean ± SD: 59.38 ± 14.36 for STEMI and 66.12 ± 10.55 for NSTEMI patients), while the age of the control group ranged from 25 to 86 years (mean ± SD: 56.4 ± 15.3). Seventy-four percent (74%) of the patients with MI and 68 (68%) of the control group were males, and 26 (26%) of the patients and 32 (32%) of the control group were females.

Platelet *GPIIIa PlA1/PlA2* polymorphic genotypes and allelic frequencies

The platelet *GPIIIa* homozygous genotype *PlA1/PlA1* was more frequent in the control group than in the patients with both STEMI and NSTEMI, while the genotypes *PlA1/PlA2* and *PlA2/PlA2* were more frequent in the patients with both types of MI. The distribution of the polymorphic genotypes, when compared among the study groups, showed a statistically significant difference (Table 1).

The regression analysis showed that the *PlA1/PlA1* genotype is significantly associated with reduced risk of both STEMI (odds ratio (OR) = 0.19; 95% confidence interval (CI): 0.09 - 0.34, P value = 0.00) and NSTEMI (OR = 0.21; 95% CI: 0.09 - 0.45,P value = 0.00); while the *PlA1/PlA2* genotype was significantly associated with increased risk of STEMI (OR = 6.0; 95% CI: 2.61 - 13.8, P value = 0.00) and NSTEMI (OR = 6.65; 95% CI: 2.69 - 16.45, P value = 0.00); the *PlA2/PlA2* genotype showed no statistically significant association with the risk of both types of MI (OR: 1.80, 95% CI: 0.70 - 4.62, P value = 0.22 for STEMI and OR: 1.29, 95% CI: 0.41 - 4.03, P value = 0.67 for NSTEMI).

The frequency of the leucine allele (*PlA1*) was 0.85 in the control group, 0.63 in the patients with STEMI, and 0.66 in the patients with NSTEMI, whereas the frequency of the proline allele (*PlA2*) was 0.15 in the control group, 0.37 in the patients with STEMI, and 0.34 in patients with NSTEMI. No deviation from Hardy-Weinberg equilibrium was observed ($\chi^2 = 0.61$, df = 2, and P value = 0.63).

Interaction of platelet *GPIIIa PlA1/PlA2* polymorphism with conventional MI risk factors

Hypertension, patients' and family history of MI, smoking, and ex-smoking were the conventional MI risk factors reported in our study group. The multivariate regression analysis showed that the *PlA1/PlA1* genotype did not interact with any of the conventional MI risk factors in patients with both types of MI, while the risk of STEMI has increased to about 14 folds in the individuals carrying the genotype *PlA1/PlA2* and have a family history of MI (OR: 13.57, 95% CI: 1.42 - 130.03, P value = 0.02). The genotype *PlA2/PlA2* was found to interact with smoking to increase the risk of NSTEMI to about 18 folds (OR: 17.63, 95% CI: 0.96 - 324.70, P value = 0.05). No interaction was found between the *GPIIIa PlA1/PlA2* genotypic variants and other MI conventional risk factors in patients with both types of MI (P value > 0.05).

Discussion

Due to the multifactorial nature of atherosclerosis, it would be too simplistic to attribute variations among individuals solely to genetic inheritance. However, identifying the genetic factors responsible for such an intricate ailment poses numerous obstacles, encompassing genetic diversity as well as interactions among genes and between genes and the environment [18].

This study investigated the association between platelet *GPIIIa PlA1/PlA2* genetic polymorphism and susceptibility to MI in non-diabetics, independently or in association with the conventional MI risk factors.

The mean age of incidence for both STEMI and NSTEMI was in the sixth and seventh decades of life, respectively; this agrees with a study conducted previously in Sudan by Ali et al (2016), which also reported a high incidence age for cardiovascular diseases [19].

The conventional MI risk factors reported among our study population were hypertension, smoking, ex-smoking, and patients' and family history of MI. This finding is consistent with the established association between hypertension and

smoking, and the heightened risk of MI [19-21].

The comparison of the *GPIIIa PlA1/PlA2* polymorphic genotypes distribution in the patients with both MI types and the control group showed a statistically significant difference. The *PlA1/PlA1* homozygous genotype was more frequent in the control group than in patients with both types of MI, while the genotypes *PlA1/PlA2* and *PlA2/PlA2* were more frequent in the patients' group. This finding agrees with that reported in young Mexicans by Santiago-German et al (2012), who reported a significant difference in the distribution of polymorphic genotypes, with a higher frequency for the *PIA1/PIA1* genotype in the control group and higher frequencies for both *PIA1/PIA2* and *PIA2/PIA2* genotypes in the patients with STEMI [22]. Also, our result was in part similar to that reported by Galasso et al (2010), who also reported a higher prevalence of the *PlA1/PlA1* genotype in the control group and a higher frequency of the *PlA1/PlA2* genotype in patients with coronary artery disease; but in contrast to our finding, they reported a higher frequency of the *PlA2/PlA2* in the control group [23], which can be due to differences in selection criteria of the control group.

The results of the present study indicate a significant association between platelet *GPIIIa PlA1/PlA2* polymorphism and susceptibility to MI. The *GPIIIa PlA1/PlA1* genotype is not a risk factor for both types of MI, but it has a protective effect. This finding agrees with many studies that concluded a lack of association between *GPIIIa PlA1/PlA1* and risk of MI, independently or in association with other known risk factors [15, 24, 25].

The present study revealed that the *GPIIIa PlA1/PlA2* heterozygous genotype is a predisposing genetic factor for MI and increases the risk of STEMI by six-fold and NSTEMI by about seven-fold. Furthermore, the *PlA1/PlA2* genotype was found to interact with the family history of MI to increase the risk of STEMI to about 14 folds. Although the frequency of *PIA2/PIA2* genotype was higher in patients with both types of MI, it was not associated with the risk of MI independently, but it increases the risk of NSTEMI about 18-fold in smokers. The frequency of the leucine allele (*PIA1*) was higher among the control group, whereas the frequency of the proline allele was higher in the patients with both types of MI. These findings suggest that the carriage of the proline allele is a risk factor for MI either independently or in combination with other factors, mainly family history and smoking. This finding is consistent with a study in Tunisia, which reported that the *GPIIIa PlA1/PlA2* genotype might be considered a significant risk factor for cardiovascular diseases in middle-aged Tunisians [26]; also, Weiss et al (1996) observed that the proline allele of the platelet *GPIIIa* increases the risk of acute coronary thrombosis by 6.2 folds in those aged less than 60 years [15]; Al-Ali et al (2008) suggested that proline allele may increase the risk of cardiovascular diseases by 2.5 folds in renal failure patients on hemodialysis [25]; Harris et al (2008) reported a significantly higher thrombosis risk (4.68) in the individuals carrying the proline allele [27]. Furthermore, Barakat et al (2001) also suggested an interaction between the *GPIII PlA1/PlA2* polymorphism and smoking in patients with NSTEMI [28].

In contrast to our finding, a study by Samani et al (1997) concluded that the *PlA2* variant of *GPIIIa* is not a significant risk factor for MI [29]. Also, Gardemann et al (1998) could not detect a difference in the distribution of allele and genotype frequencies between controls and survivors of MI [30]. The disagreement between our findings and the latter two studies can be due to differences in the inclusion criteria, as in our study we excluded diabetic patients.

Limitations of the study

A limitation of this study was the small sample size. Another study is necessary to further confirm the association between the *GPIIIa* polymorphism and susceptibility to MI, as well as interaction with other factors such as body mass index (BMI), dyslipidemia, and pharmacotherapy for hypertension.

Conclusions

Platelet *GPIIIa PlA1/PlA2* polymorphism is significantly associated with susceptibility to STEMI and NSTEMI in non-diabetics. The family history of MI and smoking increase the risk of MI in proline allele carriers. These findings may contribute to the continuous efforts of understanding the heredity of MI to help in risk assessment and improvement of preventive protocols, as well as the development of targeted antiplatelet therapies to mitigate the MI risk. However, the study's findings may need further clarification by conducting a study with a large sample size or a longitudinal cohort study.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

Informed consent was obtained from each participant before enrollment in the study.

Author Contributions

MAM collected the data, performed practical work, and analyzed data. EWA stated the study design, supervised the practical work, and wrote the draft. GMA supervised all processes, interpreted the findings, and reviewed and approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

GP: glycoprotein; MI: myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; SD: standard deviation; OR: odds ratio

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