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Genetic Polymorphism of *ITGA2* C807T Collagen Receptor Encoding Gene of Aspirin Therapy among Javanese-Indonesian Healthy Respondents

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Abstract

BACKGROUND: Aspirin is an antiplatelet drug commonly administered as primary and secondary prophylaxis to prevent thromboembolic events. However, there has been a common incidence of aspirin resistance that leads to a recurrent cerebrovascular disease. One of the causes of such event is the genetic polymorphisms of the integrin alpha-2 (ITGA2) gene that encodes the glycoprotein Ia (GPIa) receptor in the pharmacodynamics of aspirin.

AIM: This study analyzed the genetic polymorphism of ITGA2 as the GPIa collagen receptor encoding gene of aspirin therapy among healthy Javanese, the largest ethnic group in Indonesia.

METHODS: This cross-sectional study involved 100 respondents who met the inclusion criteria with their blood sample taken for DNA isolation. Identification of genetic polymorphism in the target SNPs was done using the PCR-RFLP method with 5'-CCTTAAAGCTACCGGCCCATGT-3' forward primer and 5'-TTGGCCTATTAGCACCAAAACTTACC-3' reverse primer as well as *Hpy188I* restriction enzyme to fragment the target at position 244 in the C base.

RESULTS: This study found that the dominant genotype and allele were CT (51%) and C (66.5%), respectively.

CONCLUSION: The allele frequency of *ITGA2* gene in this study was similar to that of the populations in other Asian countries. Further research regarding the effects of *ITGA2* C807T polymorphism on the pharmacodynamics of aspirin as an antiplatelet is recommended to minimize atherothrombotic events and examine its interactions as a biomarker of the risk and prognosis of some cancer types.

Introduction

As an antiplatelet, aspirin inhibits the cyclooxygenase enzyme, especially the COX-1 isoform which is expressed in a large number of tissues and catalyzes the conversion of arachidonic acid to prostaglandin G2 and prostaglandin H2. Then, through the action of thromboxane synthase, these prostaglandins are converted to thromboxane A2 (TXA2), which is a potent activator of platelet aggregation [1]. Therefore, aspirin is able to suppress platelet aggregation with superior affinity for COX1 when compared to COX2, thus causing an antiplatelet effect to occur at a low dose without an anti-inflammatory effect [2]. Despite ample evidence that supports the use of aspirin as both primary and secondary prevention of cardiovascular disease [2], it is estimated that 2–57% of those taking aspirin show a suboptimal response. Consequently, a number of individuals do not respond to the drug action and experience recurrent vascular thromboembolic events known as aspirin resistance [3].

Clinically, aspirin resistance occurs when aspirin fails to suppress the production of thromboxane A2 and subsequently induces platelet activation and aggregation processes, which increase the risk of death or further cardiac events [4]. A meta-analysis of 20 pieces of research on aspirin resistance shows a nearly 4-fold increase in the risk of further cardiac events and a 6-fold increased risk of death [5]. Some of the factors that lead to the failure of aspirin to suppress TXA2 expression and inhibit platelet aggregation are associated with genetic and non-genetic factors [6]. When patients have been adherent to medication and no other NSAIDs are taken, the genetic factor becomes one of the contributors to the response variability in aspirin administration.

Genetic variation in the form of polymorphism of the integrin alpha-2 (*ITGA2*) as the glycoprotein Ia (GPIa) encoding gene has proved to change the function

of aspirin target action as an antiplatelet. Numerous studies focusing on the polymorphism of *ITGA2* C807T gene that encodes the GPIa collagen receptor have proved its correlation with aspirin resistance. A study of Han Chinese patients with acute ischemic stroke shows that the T allele significantly correlates with aspirin resistance (OR 4.86) [7]. Similarly, a meta-analysis reveals that rs1126643 (C807T) polymorphism becomes the genetic variation associated with aspirin insensitivity [8], risk of ischemic stroke among the Asian populations [9], and risk of elevated levels of serum cholesterol [10]. In addition, a comprehensive meta-analysis of 60 studies suggests that *ITGA2* C807T with the Ser allele of HPA-3 and B allele of glycoprotein Ibα simultaneously correlates with an increased risk of ischemic stroke [11]. Pharmacogenetic research on the pharmacodynamics of aspirin that involves the Indonesian population has never been done to date. Therefore, this study aims to determine the distribution of *ITGA2* C807T allele frequency among the Indonesian population, particularly in the Javanese as the major ethnic group in Indonesia.

Materials and Methods

Research subjects

This cross-sectional study used the stored biological samples in the form of isolated DNA collected from the 3 ml of blood of 100 healthy subjects of a previous study. The respondents were categorized as Javanese according to their previous three generations of Javanese-Indonesian. This research has passed the ethical review from the Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia with protocol Number 4/Ka.Kom.Et/D/KE/XII.

Genotype analysis of ITGA2 C807T gene

The genotype analysis of the target polymorphism involved the PCR-RFLP method with forward primer 5'-CCTTAAAGCTACCGGCCCATGT-3' and reverse primer 5'-TTGGCCTATTAGCACCAAAACTTACC-3' followed by digestion of the amplicons using the *Hpy188I* enzyme. The PCR conditions for amplification included pre-denaturation at a temperature of 95°C for 2 min, 35 cycles of denaturation at the same temperature for 30 s, annealing at 57°C for 30 s, and extension at 72°C for 30 s with the final extension at 72°C for 5 min. The visualization of amplification products was prepared using agarose gel electrophoresis with 2.5% agarose concentration at 70 volts for 90 min. The digestion of 288 bp amplicon resulted in 244 bp and 44 bp fragments of wild-type CC genotype, also 288 bp, 244 bp, and 44 bp of heterozygous CT genotypes, and 288 bp of mutant TT genotype. The genotype and allele frequencies were determined based on the Hardy-Weinberg principle as follows [12], [13].

$$\text{Genotype frequency} = \frac{\text{Number of individuals with a specific genotype}}{\text{Total number of individuals}}$$

$$\text{C Allele frequency} = \frac{(2 \times \text{Number of CC Individuals}) + (\text{Number of CT Individuals})}{(2 \times \text{Total Number of Individuals})}$$

$$\text{T Allele frequency} = \frac{(2 \times \text{Number of TT Individuals}) + (\text{Number of CT Individuals})}{(2 \times \text{Total Number of Individuals})}$$

Results

There were 100 healthy respondents from Javanese-Indonesian ethnic group involved in this study of the SNPs frequency of *ITGA2* rs1126643 C>T gene, consisting of men and women in equal number. The characteristics of the research subjects are presented in Table 1.

Table 1: Characteristics of the research subjects

Patient characteristic	Male (n = 50)	Female (n = 50)
Mean age (years)	21.26 ± 1.21	21.14 ± 1.43
Mean BMI (kg/m^2)	22.73 ± 4.09	21.49 ± 3.41
Type of *ITGA2* rs1126643 C>T genotype		
CC	19	22
CT	28	23
TT	3	5
Type of *ITGA2* rs1126643 C>T allele		
C	0.66	0.67
T	0.34	0.33

BMI: Body mass index.

The subject characteristics in terms of both phenotypic factor, which includes mean age and BMI, and genotypic factor related to genetic variants in the target SNPs indicate no significant differences between men and women ($p > 0.05$). Overall, this study found that the majority of genotypic variants in the *ITGA2* rs1126643 C>T gene were CT type and C allele. Figure 1 shows the electrophoretic display of the enzyme digestion products for detecting the target polymorphism.

Discussion

The frequency of genotypic variants in *ITGA2* C807T as the GPIa protein-encoding gene does not significantly differ between the men and the women in this study. In contrast to the GPIIb-IIIa receptors, the GPIa collagen receptor shows no different expression based on sex [14]. However, differences

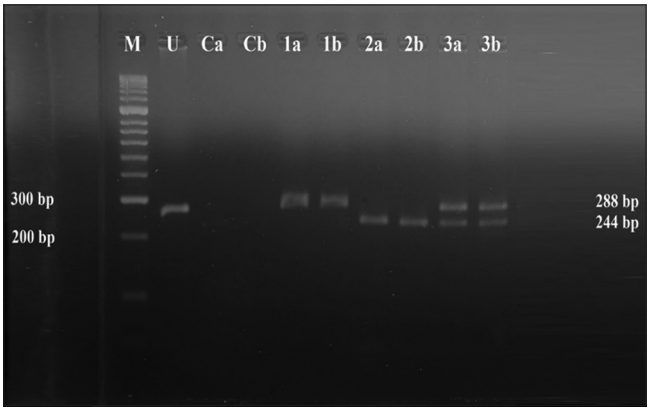

Figure 1: Visualization of Hpy188I digestion products. Lane M = 50 bp marker/ladder; lane U = undigested product/PCR product; lane C.a and C.b = negative control; lane 1a and 1b = subjects with TT genotype; lane 2a and 2b = samples with mutant (CC genotype); lane 3a and 3b = sample with heterozygote (CT genotype)

in the response to aspirin as primary cardioprotection between men and women have been discussed by a gender-specific meta-analysis [15]. Similarly, the WHI long-term study has found aspirin to be effective for primary prevention of stroke in female patients but ineffective for that of myocardial infarction (MI). In contrast, aspirin is effective as a primary prevention of MI in men. However, there is no clarity as to what causes such differences, making it necessary to probe for further explanation [16]. In addition, in conjunction with clinical studies that involve only a small number of female subjects, especially in Phase 1, and recent findings other than pharmacokinetic studies, gender-related differences have proved to influence the pharmacodynamics and pharmacogenomics of drugs, including aspirin. Consequently, before such studies are translated into a clinical setting, a gender-based approach is required to draw a feasible conclusion for both genders so as to adjust the administration of aspirin according to individual needs [17]. If further studies can provide evidence to reinforce the presence of significant differences in the pharmacokinetics and pharmacodynamics of aspirin between the two genders, then the pharmacogenomic studies of aspirin, in addition to the study designs that involve a control group and adequate sample size, are required to employ equal proportion of both genders to provide more accurate data analysis and results.

A number of studies with the same SNPs targets as this study and with the pharmacodynamic impacts of aspirin have been carried out among various populations (Table 2).

Table 2 describes the studies published as original articles with the majority of them finding no correlations between *ITGA2* C807T and an increased

Table 2: Genotype frequencies of GP1a C807T in various populations in the world

Population/ Race	Number of samples	Genotype frequency (%)			Finding	References
		CC	CT	TT		
Original article						
Javanese, Indonesia	100	41.0	51.0	8.0	The frequency of GP1a C807T mutant allele was lower than that of C allele	Present study
Caucasian	2369 patients with VTE, 1460 healthy subjects	Case 34.6 Control 36.0	Case 48.1 Control 46.7	Case 17.3 Control 17.3	There was no difference in the frequency of GP1a C807T polymorphism between VTE and the control, but there was a significantly increasing risk among 732 VTE patients with a family history of myocardial infarction and/or stroke	Kvasnicka *et al*. (2015) [18]
Han Chinese	503 patients with ST-elevation myocardial infarction	Data not shown			There was no association between *ITGA2* C807T polymorphism in the platelet receptor encoding gene and the risk of ischemic stroke and bleeding incidence	Zhang *et al*. (2016) [19]
Jordanian	584 patients	Aspirin responders 38.4 Aspirin non-responders 43.5	Aspirin responders 47.2 Aspirin non-responders 50.0	Aspirin responders 14.4 Aspirin non-responders 6.5	The GP1a C807T polymorphism was not associated with aspirin resistance	Al-Azzam *et al*. (2013) [20]
Ukrainian	54 patients with stable angina pectoris II-III and ACS with history of PCI	Aspirin responders 63.2 Aspirin non-responders 17.1	Aspirin responders 21.0 Aspirin non-responders 25.7	Aspirin responders 15.8 Aspirin non-responders 53.2	Declined sensitivity to aspirin as an antiplatelet was correlated with *ITGA2* C807T polymorphism in patients with ACS after PCI. IHD patients with T allele had a lower platelet response especially in patients who received antiplatelet therapy, including aspirin	Liakhotska (2017) [21]
Caucasian	179 stroke patients, 172 control	Stroke with 3 subtypes 44.1 Control 34.3	Stroke with 3 subtypes (CT/TT) 55.9 Control 65.7		The integrin α2 C807T polymorphism did not affect the development of ischemic stroke	Cole *et al*. (2003) [22]
German	941 patients with stable CAD	40.4	43.6	16.0	Together with rs1062535 SNPs, rs1126643 polymorphism was associated with the prognosis of cardiovascular diseases, especially in high-risk patients	Rath *et al*. (2017) [23]

(Contd...)

Table 2: ***(Continued)***

Population/ Race	Number of samples	Genotype frequency (%)			Finding	References
		CC	CT	TT		
Caucasian	286 healthy subjects, 160 patients with hereditary mucocutaneous bleeding	Data not shown	CT+TT Patients with bleeding 67.1 Control 65.6		The *ITGA2* C807T polymorphism did not significantly influence the platelet function and not correlate with the pathogenesis of bleeding incidence	Martinez *et al*. (2009) [24]
Chinese	350 patients with ischemic stroke patients 300 control	Patients 42.3 Control 46.3	Patients 39.4 Control 45.3	Patients 18.3 Control 8.3	The *ITGA2* C807T polymorphism affected ischemic stroke with the T allele apparently playing a role in increasing the cholesterol levels	Lu *et al*. (2014) [10]
Dutch	1327 patients with primary PCI who received aspirin-clopidogrel combination therapy	Group with primary event (n=86) 45.3 Group without primary event (n=1241) 34.3	Group with primary event 37.2 Group without primary event 51.1	Group with primary event 17.5 Group without primary event 13.6	Thrombotic complications during the follow-up, in the form of cardiac death or recurrent attacks of myocardial infarction, were not associated with *ITGA2* C807T polymorphism	Verchuren *et al*. (2013) [25]
Chinese	1544 patients (cohort 2) who received CABG (Coronary Artery Bypass Graft) and follow-up for 72.8 years Major adverse cardiovascular or cerebrovascular events were confirmed by a previous cohort study involving 646 patients (cohort 1) with CABG For mechanism tracking, 131 CAD patients were tested for the function of platelet aggregation, GP1a mRNA, and protein expression	Cohort 1 Case 18.8 Control 81.2 Cohort 2 Case 9.2 Control 90.8	Cohort 1 Case 23.4 Control 76.6 Cohort 2 Case 15.3 Control 84.7		The GPIa rs1126643 polymorphism increased the risk of CABG adverse events through increasing GPIa protein expression and increasing function of platelet aggregation	Liu *et al*. (2016) [26]
Czech	73 patients with acute or chronic IHD who experienced bleeding complications within 30 days after cardiac catheterization (CAG) or PCI, 331 patients without bleeding as the control	Total (404) 43.3	44.3	12.4	There was no significant association between haplotype 4 SNPs, including GP1a C807T, and increased risk of periprocedural bleeding in IHD patients who had CAG/PCI	Sionova *et al*. (2017) [27]
Pakistani	Patients who received aspirin, 23 non-responders (case), 60 responders (control)	Aspirin responders 40.0 Aspirin non-responders35.0	Aspirin responders 37.0 Aspirin non-responders 39.0	Aspirin responders 23.0 Aspirin non-responders 26.0	There was no significant difference in the genotype and allele frequencies of GPIA C807T polymorphism between the aspirin non-responders group and responders group	Mukarram *et al*. (2016) [28]
Han Chinese	97 patients with acute ischemic stroke; aspirin sensitivity (AS) group with 54 subjects, aspirin resistance (AR) group with 43 subjects	AS 42.6 AR 27.9	AS 48.1 AR 53.5	AS 9.3 AR 18.6	The SNPs of GPIa C807T gene were correlated with aspirin resistance in Han Chinese women	Wang *et al*. (2018) [7]
Japanese	110 healthy subjects	39.1	47.3	13.6	The GPIA C807T polymorphism was not involved in the laboratory aspirin resistance according to the platelet aggregation parameter	Fujiwara *et al*. (2007) [29]
Chinese	307 patients with gastric cancer (case), 307 control	Case 45.9 Control 55.4	Case 44.0 Control 36.8	Case 10.1 Control 7.8	The subjects with (CT+TT) variants had a significantly higher risk of gastric cancer	Chen *et al*. (2011) [30]
Caucasian	118 patients with idiopathic sudden sensorineural hearing loss (iSSNHL), 161 control	Patients with iSSNHL 35.6 Control 52.2	Patients with iSSNHL 52.5 Control 40.4	Patients with iSSNHL 11.9 Control 7.4	The prevalence of T allele was significantly higher in the case group than in the control group. There was a significant correlation between TT homozygous variant and the low probability of recovery	Ballesteros *et al*. (2012) [31]
Russian	46 full-term newborns with arterial and venous thrombosis, 57 healthy newborns as the control	Case 45.6 Control 56.1	Case 32.6 Control 42.1	Case 21.8 Control 1.8	Together with other polymorphisms, the SNPs of *ITGA2* C807T gene became a criterion to identify the high-risk group of arterial and venous thrombosis among newborns	Filippova *et al*. (2020) [32]
Russian	446 preeclampsia patients	32.5	48.4	19.1	The TT variant in *ITGA2* C807T gene was apparently correlated with increased blood pressure among women with preeclampsia during the last trimester of pregnancy	Golovchenko *et al*. (2020) [33]
German	433 colorectal cancer patients 433 healthy subjects as the control	Patient 40.6 Control 32.9	Patient 45.6 Control 48.8	Patient 13.8 Control 18.3	The *ITGA2* C807T polymorphism was associated with a reduced risk of colorectal cancer. In the codominant model, the odds ratio of 807-T allele was 0.77.	Gerger *et al*. (2009) [34]
Malaysian	300 patients with nasopharyngeal carcinoma (NPC)	57.0	34.3	8.7	The TT genotype in *ITGA2* C807T gene has worse all-cause survival compared to the CC genotype. The polymorphism could serve as a biomarker of NPC prognosis.	Ban *et al*. (2018) [35]
Greece	32 fetuses with fetal growth restriction (FGR) and the mothers 18 fetuses as the control at corresponding gestational age and the mothers	FGR 46.9 Control 50.0	FGR 43.7 Control 50.0	FGR 9.4 Control 0	There was no correlation between SNPs of *ITGA2* C807T and FGR	Simou *et al*. (2017) [36]

(Contd...)

Table 2: ***(Continued)***

Population/ Race	Number of samples	Genotype frequency (%) CC	CT	TT	Finding	References
Systematic review/meta-analysis						
Category			Subjects		Findings	Reference
Meta-analysis of 15 studies with a case–control design or cohort design consisting of 11 studies in Asian race and four studies involving Caucasians			2242 case and 2408 control		There was a relationship between *ITGA2* C807T polymorphism and the risk of ischemic stroke in all Asian population and hospital-based population, but not in the Caucasian population and non-hospitalized individuals.	Wu *et al*. (2014) [9]
Meta-analysis of 16 studies with case–control, nested case–control, or cohort designs			2586 case and 2698 control with 16 studies in Asian race and Caucasians		Together with the other two polymorphisms, the TT genotype or T allele in GPIa C807T was correlated with the increased risk of ischemic stroke.	Liu *et al*. (2017) [11]
Meta-analyses of seven studies with case–control, nested case–control, or cohort designs			209 patients receiving aspirin and 676 control		The *ITGA2* rs1126643 SNPs indicated a significant correlation with aspirin insensitivity. The subgroup analysis showed that these SNPs were potentially higher among patients with semi-resistance aspirin than in the aspirin resistance group	Weng *et al*. (2013) [8]

VTE: Vein thromboembolism, CAD: Coronary artery disease, ACS: Acute coronary syndrome, PCI: Percutaneous coronary intervention.

risk of some events, including ischemic stroke, aspirin insensitivity, vein thromboembolism, recurrent attacks of MI, and bleeding. In contrast to the three meta analyses, which draw relatively similar conclusion that SNPs are associated with the incidence of ischemic stroke and aspirin insensitivity, another meta-analysis conducted before 2010 shows that such polymorphisms are not a risk factor, either alone or in combination with other major cardiovascular risk factors, of the incidence of coronary artery disease [37]. It is interesting that nearly all of the studies linking *ITGA2* rs1126643 C>T to clinical conditions other than cerebrocardiovascular disease have found significant correlations, including those associated with some types of cancer.

It is acknowledged that the ITGA gene or popularly known as integrin $\alpha 2\beta 1$ is widely expressed in the cells associated with both the basement membrane (keratinocytes, epithelial cells, and endothelial cells) and the interstitial Collagen-I-rich matrix, such as fibroblasts, T cells, myeloid cells, and megakaryocytes and/or platelets. In fact, ITGA is the only collagen-binding integrin which is expressed on platelets, thus leading to a careful definition of its important role in platelet function and homeostasis [38]. The *ITGA2* gene encodes GPIa, a receptor with high affinity for platelet activation, by triggering adhesion thus causing polymorphisms in the *ITGA2* gene to be able to affect the risk of thrombosis as shown by the studies in Table 2. In addition, *ITGA2* C807T SNPs have also proved to be associated with susceptibility to cancer and its prognosis. Therefore, the significant role of *ITGA2* in various diseases, including cancer, indicates its potential to become a novel therapeutic target [39].

The high frequency of mutant allele in *ITGA2* C807T (>30%) among the Java-Indonesia population in this study requires further research along with the efforts to reduce the incidence of cardiovascular disease and the risk of cancer through health promotion strategies for cancer prevention in groups of patients with high susceptibility.

Conclusion

The allele frequency in the *ITGA2* C807T gene found among the healthy Javanese-Indonesian subjects in this study is a novelty. The findings reveal that the frequency of the T allele in the *ITGA2* C807T gene is lower than that of the C allele, which is 33.5%. Further research is necessary to analyze the correlation between such polymorphisms and their implications for the pharmacodynamic variability of aspirin as well as the risk and the prognosis of some cancer types.

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