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'-TTGGCCTATTAGCACAAAACCT-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

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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'-CCTAAAGCTACCGCCCATGT-3' and reverse primer 5'-TTGGCCTATTAGCACTAACC-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].

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

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

T Allele frequency = \frac{(2 \times \text{Number of TT 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.

| Patient characteristic | Male (n = 50) | Female (n = 50) |
|------------------------|--------------|----------------|
| Mean age (years)       | 21.26 ± 1.21 | 21.14 ± 1.43   |
| Mean BMI (kg/m²)       | 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        | T        |
|------------------------------------|---------|---------|
| Frequency                          | 0.66    | 0.34    |

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
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         |
| Indonesian       | 100              | 41.0                   | 51.0    | 8.0        | 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 | | Declined sensitivity to aspirin as an antplatelet 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 antplatelet therapy, including aspirin. | 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 | | Declined sensitivity to aspirin as an antplatelet 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 antplatelet therapy, including aspirin. | Liahotiska (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 | | | Cole et al. (2003) [22] |
| German           | 941 patients with stable CAD | 40.4 | 43.6 | 16.0 | The integrin α2 C807T polymorphism did not affect the development of ischemic stroke. Together with rs1062635 SNPs, rs1126643 polymorphism was associated with the prognosis of cardiovascular diseases, especially in high-risk patients. | Rath et al. (2017) [23] |
Table 2: (Continued)

| Population/Race | Number of samples | Genotype frequency (%) | Finding | References |
|-----------------|-------------------|------------------------|---------|------------|
| Caucasian       | 286 healthy subjects, 160 patients with hereditary mucocutaneous bleeding | Data not shown | CT+TT Patients with bleeding 67.1 | 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=886) 45.3 Group without primary event (n=1241) 34.3 | Group with primary event 37.2 Group without primary event 51.1 | 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 | Venco 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 51.2 Cohort 2 Case 9.2 Control 90.8 | Cohort 1 Case 23.4 Control 76.6 Cohort 2 Case 15.3 Control 84.7 | There was no significant association between haplotype 4 SNPs, including GP1a C807T, and increased risk of periprocedural bleeding in IHD patients who had CABG/PCI | 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 difference in the genotype and allele frequencies of GPIA C807T polymorphism between the aspirin non-responders group and responders group | Simova et al. (2017) [27] |
| 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 | The SNPs of GPIA C807T gene were correlated with aspirin resistance in Han Chinese women | Wang et al. (2018) [7] |
| Japanese        | 110 healthy subjects | Aspirin responders 40.0 Aspirin non-responders35.0 | Aspirin responders 37.0 Aspirin non-responders 39.0 Aspirin responders 23.0 Aspirin non-responders26.0 | The GPIA C807T polymorphism was not involved in the laboratory aspirin resistance according to the platelet aggregation parameter | Fujikawa et al. (2007) [29] |
| Chinese         | 307 patients with gastric cancer (case), 307 control | Aspirin responders 40.0 Aspirin non-responders35.0 | Aspirin responders 37.0 Aspirin non-responders 39.0 Aspirin responders 23.0 Aspirin non-responders26.0 | There was no significant association between CT+TT variants and a 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 | 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 | Ballesieros et al. (2012) [31] |
| Russian         | 46 full-term newborns with arterial and venous thrombosis, 57 healthy newborns as the control | Case 46.6 Control 53.4 | Case 52.6 Control 47.4 | 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 | Aspirin responders 40.0 Aspirin non-responders35.0 | Aspirin responders 37.0 Aspirin non-responders 39.0 Aspirin responders 23.0 Aspirin non-responders26.0 | 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 53.9 | Patient 45.6 Control 48.8 | The ITGA2 C807T polymorphism was associated with a reduced risk of colorectal cancer. In the colonoscopy model, the odds ratio of 807-T allele was 0.77. | Genger et al. (2009) [34] |
| Malaysian       | 300 patients with nasopharyngeal carcinoma (NPC) | Aspirin responders 40.0 Aspirin non-responders35.0 | Aspirin responders 37.0 Aspirin non-responders 39.0 Aspirin responders 23.0 Aspirin non-responders26.0 | 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 | Control 50.0 | Control 55.0 | There was no correlation between SNPs of ITGA2 C807T and FGR | Simo et al. (2017) [36] |
|               | 18 fetuses as the control at corresponding gestational age and the mothers | | | | |

(Contd...)
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 α2[11] 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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