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Allele Frequency of Carbamazepine Major Efflux Transporter Encoding Gene *ABCB1* C3435T among Javanese-Indonesian Population

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Abstract

BACKGROUND: Genetic variations in ABCB1 gene that encodes P-glycoprotein, the main transporter in the efflux of carbamazepine (CBZ) from the brain cells, can lead to pharmacodynamic and pharmacokinetic variability. Polymorphism of C3435T is widely known to cause protein overexpression that contributes to an increased risk of CBZ resistance.

AIM: This study determined the allele frequency distribution of ABCB1 C3435T gene in healthy subjects of the Javanese population as a major ethnic group in Indonesia.

METHODS: This cross-sectional study involved 100 healthy volunteers who fulfilled the inclusion criteria. The genotype analysis to detect polymorphism in the targets employed the polymerase chain reaction-restriction fragment length polymorphism method with 5'-TGCTGGTCCTGAAGTTGATCTGTGAAC-3' as the forward primer and 5'-ACATTAGGCAGTGACTCGATGAAGGCA-3' as the reverse primer.

RESULTS: The frequency of subjects with C allele in *ABCB1* C3435T gene reached 53%, higher than that with T allele.

CONCLUSION: This finding was nearly the same as that in studies of the populations in China, Turkey, and four countries in the South European continent. It is recommended to conduct further research on the correlation between C3435T polymorphism and CBZ dose variability to provide a comprehensive approach to epilepsy management in patients receiving CBZ.

Introduction

Epilepsy is the most prevalent chronic neurological disorder that affects at least 50 million people globally. It is characterized by periodic and unexpected seizures [1]. The prevalence in developing countries is higher than in developed countries; for example, the prevalence of epilepsy in Indonesia ranges between 5 and 74 per 1000 people. The best therapy in the management of epilepsy hitherto is using antiepileptic drugs (AEDs) [2].

Carbamazepine (CBZ) is a tricyclic compound used as the first-line AED for focal seizures, secondary generalized seizures, and tonic-clonic seizures [2]. CBZ is not only effective but also relatively inexpensive, making it listed in the AED monotherapy choices of the National Formulary since 2013 and available up to primary health-care facilities [3]. However, in addition to the risk of allergic reactions, CBZ is an AED with a narrow therapeutic range and often causes variations in pharmacokinetics and clinical response. Such variations occur due to polymorphism in the protein-encoding gene that plays a role in bioavailability and clinical response [4]. A number of pharmacogenetic studies of CBZ have been conducted to analyze genetic variants that strongly correlate with the variability of pharmacokinetics, clinical response, and adverse drug reactions (ADR). Regarding the polymorphism of *HLA-B*1502* allele with the hazardous side effect named Stevens-Johnson Syndrome [5], research has been performed by involving the Indonesian population, with a frequency of mutant variant of 11.6% [6].

In addition to ADR risk, therapy failure due to CBZ resistance becomes another serious issue. It is estimated that approximately 30–40% epileptic patients experience AED resistance that leads to uncontrolled seizures despite the use of CBZ within the therapeutic

dose range [7], [8]. Furthermore, the maintenance dose of epileptic patients in monotherapy reaches 10-fold variety, indicating a wide interpatient variability of clinical response [9]. Among the contributing factors is the genetic polymorphism in the major CBZ efflux transporter named P-glycoprotein (P-gp) which is also expressed in the blood-brain barrier (BBB) [10]. Various studies have proved that the genetic variations in *ABCB1* C3435T gene as a P-gp encoder lead to CBZ resistance. A number of studies involving epileptic patients in Chinese, Japanese, and Caucasian populations found a positive correlation between such polymorphism and CBZ resistance or variations in CBZ plasma concentration [11], [12], [13]. Therefore, this study aims to determine the allele frequency distribution of *ABCB1* C3435T gene among the Javanese population, the largest ethnic group in Indonesia.

Pharmacogenetic understanding and studies of epilepsy therapy can provide important basic information for the development and implementation of genetic screening in making a decision on epilepsy therapy as well as become the basis for patient individualized medicine. This study is a section of prospective research on AED pharmacogenetics among the Indonesian population with epilepsy. Analysis of genetic variants in the target P-gp encoding gene is important to provide information on the genetic variation profile among the Indonesian population of which implications for individual therapeutic dose and clinical response to CBZ use can be further examined.

Methods

Research subjects

The DNA was extracted from 3 ml blood of 100 healthy respondents aged 18–23 years. The category of respondents was those from Javanese ethnic group identified based on their three previous generations. This study has obtained ethical clearance from the Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia with the protocol No. 35/Ka.Kom.Et/70/KE/XII.

Genotyping

Genotyping of *ABCB1* C3435T was conducted through the polymerase chain reaction (PCR) method using 5'-TGC TGG TCC TGA AGT TGA TCT GTG AAC-3' as the forward primer and 5'-ACA TTA GGC AGT GAC TCG ATG AAG GCA-3' as the reverse primer followed by restriction fragment length polymorphism. PCR conditions for amplification included initial denaturation at 95°C for 2 min, 35 denaturation cycles at the same temperature for 30 s, annealing at 55°C for 30 s, extension at 72°C for 30 s, and final extension at 72°C for 5 min. The amplification products were visualized using agarose gel electrophoresis with 1.5% agarose concentration at 100 volts for 30 min. The PCR products (248 bp) were digested using *MboI* enzyme that identified and cut |GATC sequence in the amplicon. The digestion of amplification products yielded 16 bp, 60 bp, and 172 bp fragments of CC genotype, 16 bp, 60 bp, 172 bp, and 232 bp of CT genotype, and 16 bp and 232 bp of TT genotype.

The genotype and allele frequencies were determined based on the data of previous studies [11], [12], [13], [14] that used Hardy–Weinberg's law as follows [15], [16]:

$$\text{Genotype frequencies} = \frac{\text{A given number of alleles in the population}}{\text{Total number of alleles in the population}}$$

Meanwhile, the allele frequencies were determined using the following formula:

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

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

f (C): C allele frequency
f (T): T allele frequency

Results and Discussion

A total of 100 healthy respondents of Javanese-Indonesian descent participated in the *ABCB1* C3435T gene genotyping with the same numbers of male and female respondents. The research subject characteristics are described in Table 1.

Table 1: Characteristics of the subjects in *ABCB1* C3435T genotyping

Patient characteristic	Male (50)	Female (50)
Average age (years)	21.3 ± 1.2	21.1 ± 1.4
Average BMI (kg/m^2)	22.7 ± 4.1	21.5 ± 3.4
Types of *ABCB1* C3435T genotype		
CC	14	10
CT	29	29
TT	7	11
Types of *ABCB1* C3435T allele		
C	57	49
T	43	51

BMI: Body mass index.

This study found that the frequencies of genotypic variation of both male and female respondents were insignificantly different. Although it is acknowledged

that gender and genetic variation frequencies are not correlated, P-gp expression and function indicate gender variations at the molecular level [17]. Therefore, in a pharmacogenomic study targeting polymorphism in *ABCB1* genes that encode P-gp protein, in addition to employing a prospective technique and adequate sample size [18], taking comorbidity factors into account, and using other drugs of P-gp inducer or inhibitor [19], and it is necessary to involve equal numbers of male and female patients to provide more accurate data analysis and results. Men and women have differences not only in P-gp expression and function but also in CBZ clearance, with even a significant difference level, in an infusion therapy [20].

Overall, the findings showed that the frequencies of CC, CT, and TT genetic variation in *ABCB1* C3435T (rs1045642) were 24%, 58%, and 18%, respectively. Research with the same polymorphism targets as this study has been widely performed by involving a variety of populations and various races (Table 2.)

The electrophoretic display of enzyme digestion for the detection of target polymorphism in this study is shown in Figure 1.

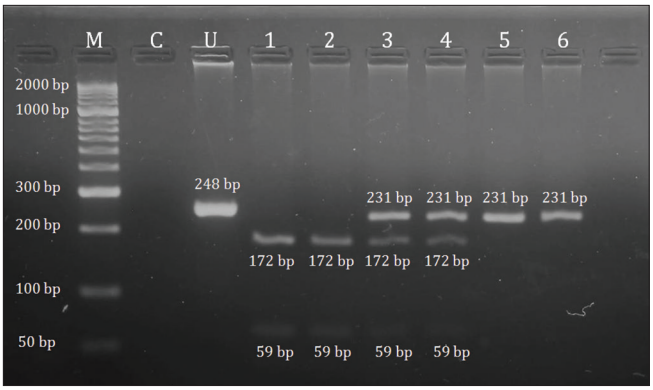

Figure 1: Electrophoretic display of genotypic variations in the target SNPs. Lane M = marker of 50 bp; lane C = negative control; lane U = undigested; lane 1 and 2= CC homozygote/wild-type (172 bp and 59 bp); lane 3 and 4= CT heterozygote (231 bp, 172 bp, and 59 bp); lane 5 and 6= TT homozygote (231 bp). SNPs: Single nucleotide polymorphisms

Numerous studies (Table 2) have linked genetic variations in P-gp encoding gene *ABCB1* to mRNA stability variations [10], the risk of epilepsy, CBZ resistance, and therapeutic dose requirements. A study involving 738 subjects in South India showed that *ABCB1* C3435T increased the risk of mesial temporal lobe epilepsy with hippocampal sclerosis [31]. In addition, a study of 84 Chinese epileptic patients who received CBZ monotherapy and 210 Chinese patients who received CBZ for at least 1 month found that *ABCB1* 3435-TT had a lower CBZ plasma concentration, and the *ABCB1* 3435CC group showed higher CDR_{CBZ} (concentration: Dose ratio, i.e., the ratio of measured CBZ concentration to the daily maintenance dose in mg/kgBW) than the 3435CT type [13], [21]. Other studies of 315 epileptic patients at the National Hospital for Neurology and Neurosurgery in London as well as 210 Japanese patients with epilepsy who were given CBZ for more than 2 years indicated different risks of CBZ resistance. The first study found that patients with CC genotype had a higher drug resistance compared to the group of TT genotype with 2.66 odds ratio (OR) and 1.32–5.38 confidence interval (CI) while the second study revealed that the TT genotype group was more prone to CBZ resistance instead (OR: 3.64, CI: 1.16–11.39) [11], [12]. Contradictory results were shown by two studies, each of which involved 97 epileptic patients with CBZ monotherapy and 174 healthy volunteers and 34 patients and 81 healthy subjects, in which no correlation was found between *ABCB1* C3435T and either CBZ resistance or clinical response to AED [14], [29]. These varied results of studies that involved different ethnic groups or races should consequently consider the study of *ABCB1* haplotype or diplotype that represents the functional unit of the gene [11]. Meanwhile, a systematic review and meta-analysis of 13 studies involving a total of 454 patients with AED-resistant epilepsy and 282 response-to-AEDs indicated that TT genotype of *ABCB1* C3435T played an important role in the incidence of refractory epilepsy [49].

The ATP-binding cassette transporter is widely known as the largest group of transmembrane transporters expressed in various tissue barriers including in the brain capillaries that construct the BBB, localized to the endothelial layer which can limit the entry of lipophilic drugs into the brain and express substances, such as β-amyloid, from neuroparenchyma. P-gp pushes xenobiotics from the intracellular part back to the capillary lumen, thus maintaining BBB integrity and reducing drug accumulation in the cerebral region. Since P-gp transporter is highly expressed in BBB, the polymorphism in *ABCB1* gene as a P-gp encoder that influences the level of expression and function can directly affect the brain uptake as well as extrusion of AEDs, including CBZ. P-gp overexpression has been proven to play an important role in a pharmacoresistant incidence in epilepsy through decreased drug concentrations in the brain even though with a plasma therapeutic concentration [53].

Since P-gp is extensively expressed not only in BBB but also in various body tissues including in small intestine and large intestine, adrenal glands, liver, kidney, placenta, and capillary endothelial cells of testes, P-gp also plays a role in the absorption, distribution, and excretion of numerous drugs as its substrates, and its function can be influenced by the presence of inhibitor drugs. A number of studies have also found the influence of the target polymorphism in this study on pharmacokinetic variations, clinical response, and risk factors of cancer. C3435T polymorphism has also been proven to cause variations in the concentrations, dose requirements, and clinical response of the drugs that function in the central nervous system, such as phenobarbital, opioids, and aripiprazole [22], [36], [44]. Similarly, some studies found a significant influence of such polymorphism on

Table 2: Genotype frequencies of *ABCB1* C3435T in different ethnic populations

Population/ethnicity	Sample size	Genotype frequencies n (%)			Findings	References
		CC	CT	TT		
Original article						
Javanese, Indonesian	100	24 (24.00)	58 (58.00)	18 (18.00)	The mutant allele frequency of *ABCB1* C3435T (47%) was lower than that of C allele	The present study
Chinese	84	30 (35.71)	39 (46.43)	15 (17.86)	T allele was found at 41.1%. This allele correlated with the decreased plasma concentration of CBZ in Chinese patients with epilepsy	Meng *et al*. (2011) [13]
Turkish	97	29 (29.90)	55 (56.70)	13 (13.40)	T allele frequency reached 41.8%. There was no significant correlation between MDR1 (C3435T) polymorphism and CBZ resistance among patients with epilepsy in Turkey	Ozgon *et al*. (2008) [14]
Japanese	210	70 (33.33)	92 (43.81)	48 (22.86)	The mutant allele frequency of C3435T (44.8%) was lower compared to that of C allele. Epileptic patients with T allele and mutant TT variant genotype were more likely to experience CBZ resistance	Seo *et al*. (2006) [11]
Caucasian	315	73 (23.17)	169 (53.66)	73 (23.17)	The frequency of T allele was identical with that of C allele in *ABCB1* C3435T. If compared to patients with antiepileptic drug response, those with antiepileptic drug resistance had CC genotype in *ABCB1* 3435 as opposed to TT genotype	Siddiqui *et al*. (2003) [12]
Chinese	210	68 (32.38)	112 (53.33)	30 (14.29)	T allele frequency was 41.0%. The study found that *ABCB1* c.3435C>T was significantly associated with the ratio of CBZ concentration to dose from CBZ and its primary metabolites in Chinese patients with epilepsy	Zhu *et al*. (2014) [21]
Chinese	112	45 (40.18)	49 (43.75)	18 (16.07)	The mutant allele frequency of C3435T (37.9%) was lower than that of C allele. If cancer patients with TT genotype in *ABCB1* suffered pain, they required a higher dose of opioid compared to those with CC/CT type	Gong *et al*. (2013) [22]
Han Chinese	292	103 (35.28)	151 (51.71)	38 (13.01)	T allele frequency was found at 38.9%. The *ABCB1* rs1045642 gene did not correlate with the therapeutic response of antidepressants (both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) in Han Chinese patients with depression	Shan *et al*. (2019) [23]
Han Chinese	185	74 (40.00)	82 (44.32)	29 (15.68)	T allele was 37.8%. Genotypic variation in rs1045642 did not influence the efficacy of etanercept in Han Chinese patients with ankylosing spondylitis	Yan *et al*. (2017) [24]
Han Chinese	236	58 (24.58)	47 (19.91)	131 (55.51)	Different from the finding of this study, the mutant allele frequency of C3435T (65.5%) was higher than that of C allele. There was no significant difference in the dose of sufentanil for Han Chinese patients who suffered pain due to lung cancer	Zhao *et al*. (2019) [25]
Taiwanese	112	29 (25.89)	52 (46.43)	31 (27.68)	T allele was found at 50.9%. Both the baseline score of Hamilton Depression Rating Scale and that of week 6 in antidepressant therapy were insignificantly different among the *ABCB1* C3435T genotypic variance of Taiwanese patients with major depressive disorder	Chang *et al*. (2015) [26]
Japanese	154 (healthy subjects) 48 (patients with CRC) 47 (patients with ESCC)	55 (35.72) 14 (29.17) 11 (23.40)	73 (47.40) 28 (58.33) 28 (59.58)	26 (16.88) 6 (12.50) 8 (17.02)	The mutant allele frequency of C3435T was higher than that of C allele. No significant difference was found in the estimation of MDR1 haplotype frequency between Japanese healthy subjects (n=154) and patients with CRC as well as ESCC	Komoto *et al*. (2006) [27]
Turkish	54	19 (35.19)	22 (40.74)	13 (24.07)	T allele was found at 44.4%. The study found that the distributions of CC genotype and C allele in *ABCB1* C3435T were significantly different between Turkish patients with major depressive disorder and healthy subjects (n=70). However, *ABCB1* C3435T polymorphism did not influence the clinical response to citalopram	Ozbey *et al*. (2014) [28]
Iranian	115 (34 patients, 81 healthy subjects)	24 (20.87)	58 (50.43)	33 (28.70)	Contrary to our findings, the mutant allele frequency of C3435T (53.9%) was higher than that of C allele. The haplotype frequency estimation (including *ABCB1* C3435T) did not indicate any significant difference between patients and the control group	Hosseini *et al*. (2018) [29]
Egyptian	220 (120 patients, 110 healthy subjects as control group)	26 (11.82)	141 (64.09)	53 (24.09)	T allele frequency was at 56.1%. The CT genotype in MDR1 gene C3435T correlated with the poor clinical outcomes in Egyptian pediatric patients with acute lymphoblastic leukemia	Talaat *et al*. (2018) [30]
South Indian	460 patients	24 (5.22)	245 (53.26)	191 (41.52)	Different from our findings, the mutant allele frequency of C3435T (68.2%) was higher than that of C allele. This cohort study found that the variants in *ABCB1* (including C3435T) did not correlate with antiepileptic drug resistance. However, *ABCB1* C3435T polymorphism was associated with the risk of developing epilepsy in patients with mesial temporal lobe epilepsy with hippocampal sclerosis	Balan *et al*. (2014) [31]
Roman and Hungarian	465; 503 healthy subjects	Roman 124 (26.67) Hungarian 112 (22.27)	Roman 234 (50.32) Hungarian 252 (50.10)	Roman 107 (23.01) Hungarian 139 (27.63)	There was a significant difference in the T allele frequency of MDR1 between Roman population (48.2%) and Hungarian people (52.7%). The T allele frequency in our study was found to be comparable with that of Roman population	Sipeky *et al*. (2011) [32]
Polish	171 (71 patients, 100 healthy subjects)	37 (21.64)	76 (44.44)	58 (33.92)	T allele distribution was at 56.1%. 1236T-2677G-3435T haplotype could provide a protective effect against bullous pemphigoid	Rychlik-Sych *et al*. (2018) [33]
Polish	90	15 (16.67)	43 (47.78)	32 (35.55)	T allele distribution (59.4%) was higher than that of C allele. C3435T polymorphism in *ABCB1* gene strongly correlated with predisposition to depression, severity of depression symptoms, and effectiveness of antidepressants	Jeleń *et al*. (2015) [34]
Romanian	74	14 (18.92)	37 (50.00)	23 (31.08)	T allele frequency was 56.1%. *ABCB1* C3435T polymorphism did not influence the plasma concentration of valproate or dose adjustment with reference to valproate concentration among Romanian patients with epilepsy	Sabin *et al*. (2016) [35]
Croatian	60	16 (26.67)	31 (51.66)	13 (21.67)	Similar to our finding, this study also found a lower T allele frequency (47.5%) as opposed to that of C allele. C3435T polymorphisms in *ABCB1* gene influenced the concentration ratio of phenobarbital in serum/cerebrospinal fluid among Croatian patients with idiopathic primary generalized epilepsy who received phenobarbital monotherapy	Basic *et al*. (2008) [36]

(*Contd...*)

Table 2: (*Continued*)

Population/ethnicity	Sample size	Genotype frequencies n (%)			Findings	References
		CC	CT	TT		
Original article						
Spanish	74	21 (28.38)	33 (44.59)	20 (27.03)	T allele (49.3%) was found to be less than C allele in *ABCB1* C3435T. In addition to the risk of developing hyperbilirubinemia, the plasma concentration of atazanavir was significantly higher in HIV-infected patients with CC genotype compared to those with CT or TT variants	Nóvoa *et al*. (2006) [37]
Portuguese	160	56 (35.00)	73 (45.62)	31 (19.38)	T allele in *ABCB1* C3435T was found at 42.2%. This allele provided protection against major depression in male subjects	Santos *et al*. (2013) [38]
	937	260 (27.75)	482 (51.44)	195 (20.81)	T allele (46.5%) was lower than C allele in *ABCB1* C3435T. Patients with minor T allele in *ABCB1* rs1045642 achieved better clinical outcomes as opposed to the CC genotype group undergoing gemtuzumab ozogamicin (GO) therapy and risk of relapse. Consistent results were also obtained when the genotype group was compared by GO and No-GO arms	Children's Oncology Group AAML0531 Trial Rafiee *et al*. (2019) [39]
Caucasian	40	15 (37.50)	18 (45.00)	7 (17.50)	T allele distribution was found at 40.0%. Polymorphism of rs1045642 in *ABCB1* gene significantly correlated with increased blood pressure in 1 year after patients had a kidney transplant	Bouatou *et al*. (2018) [40]
Caucasian 4 case-control studies	395 patients dan 418 healthy subjects as control group	207 (25.46)	403 (49.57)	203 (24.97)	T allele in *ABCB1* C3435T was found at 49.8%. MDR1 C>T polymorphism was not associated with the risk of multiple myeloma	Razi *et al*. (2018) [41]
Caucasian	100	17 (17)	53 (53)	30 (30)	T allele (56.5%) was found higher compared to C allele in *ABCB1* C3435T. The highest antihypertensive effect of amlodipine with minimum incidence of reactions was found in the Caucasian patient group with Stage I-II hypertension and TT genotype	Sychev *et al*. (2018) [42]
Russian	60	15 (25)	29 (48.33)	16 (26.67)	T allele distribution in *ABCB1* C3435T was 50.8%. Polymorphism of rs1045642 in *ABCB1* gene made a major contribution to the safety of dabigatran in patients undergoing knee surgery	Sychev *et al*. (2018) [43]
Japanese	233	73 (31.33)	160 (68.67)			Hattori *et al*. (2018) [44]
Angolan	101	77 (76.24)	16 (15.84)	8 (7.92)	T allele distribution was at 15.8%. *ABCB1* c.3435C>T drug transporter influenced the clinical outcomes of artemether-lumefantrine in malaria patients without complications	Kiaco *et al*. (2017) [45]
Polish	196	46 (23.47)	83 (42.35)	67 (34.18)	T allele (55.4%) was higher than C allele in *ABCB1* C3435T. *ABCB1* C3435T polymorphism was not a major factor in susceptibility to peptic ulcer but a risk factor in developing *Helicobacter pylori* infection in male patients	Sałagacka *et al*. (2011) [46]
Spanish	473	138 (29.18)	243 (51.37)	92 (19.45)	Similar to our study, this research also found T allele distribution (45.1%) that was lower than that of C allele. *ABCB1* C3435T polymorphism influenced the elimination of several antipsychotics and antidepressants	Saiz Rodríguez *et al*. (2018) [47]
Systematic review/meta-analysis						
Category		Sample			Findings	References
Meta-analysis in studies of Caucasian and Asian		8604			*ABCB1* C3435T polymorphism was a genetic marker for antiepileptic drug resistance associated with Caucasian population but not among Asian people	Li *et al*. (2015) [48]
Systematic review and meta-analysis of 13 studies		736			TT genotype in *ABCB1* C3435T played a role in refractory epilepsy	Chouchi *et al*. (2017) [49]
Moroccan case-control study and meta-analysis		Various populations in the meta-analysis; 60 patients and 68 healthy women in the case-control study			The implication of C3435T variant on the risk of breast cancer was ethnicity-dependent. The case-control study found no evidence that such polymorphism played an important role in susceptibility to breast cancer	Tazzite *et al*. (2016) [50]
Meta-analysis of 17 studies		2431 cases and 3028 controls from various countries and ethnic groups			C3435T polymorphism in *ABCB1* gene was associated with an increased risk of leukemia	Ma *et al*. (2015) [51]
Meta-analysis of 12 studies		Varied ethnic groups			C3435T polymorphism in *ABCB1* gene could become a risk factor in major adverse cardiovascular events among patients who received clopidogrel, and TT homozygote had a lower hemorrhage risk than CC homozygote	Su *et al*. (2012) [52]

CBZ: Carbamazepine, CRC: Colorectal cancer, ESCC: Esophageal squamous cell carcinoma, MDR: Multidrug resistance.

the pharmacokinetics of antiviral atazanavir and the clinical outcomes of artemether-lumefantrine antimalarial regimen [37], [45] as well as the chemotherapy clinical outcomes in pediatric patients with leukemia [30], [39]. Furthermore, C3435T rs1045642 polymorphism has even been proven to correlate significantly with amlodipine efficacy and safety, patients' blood pressure after kidney transplantation, and the safety of dabigatran as a thrombin inhibitor [40], [42], [43]. Not only associated with pharmacogenomics because of their function as part of cellular defense mechanism, but C3435T polymorphism also has a significant clinical correlation as a predisposition to depressive disorders [28], [34], [38]. A similar finding was also found in a study of haplotype involving such polymorphism with the risk of colorectal and esophageal cancer and in a systematic review and meta-analysis regarding the genetic susceptibility to multiple myeloma [27], [41].

These relatively high frequencies of C3435T mutant allele among the Javanese-Indonesian population require further studies. This is in accordance with the lacking involvement of the Indonesian population in new drug development for a drug selection approach, availability of more appropriate therapeutic doses, and health promotion strategies to prevent cancer among vulnerable subject groups.

Conclusion

The findings in the study of *ABCB1* rs1045642 C>T allele frequencies among healthy volunteers of Javanese-Indonesian ethnic group become a novelty

in the preliminary study of CBZ pharmacogenetics study that has never been conducted. The results indicate that the frequency of subjects with T allele in *ABCB1* C3435T gene was lower than that with C allele, reaching 47%. Further research is recommended to analyze the correlation between such polymorphism and their implications for pharmacokinetic variability as well as CBZ resistance.

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