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Research article

Frequencies of HLA-B alleles in Indonesian Malay Ethnic

Rika Yuliwulandari [a,*], Kinasih Prayuni [b], Kencono Viyati [b,c], Surakameth Mahasirimongkol [d], Nuanjun Wichukchinda [d]

[a] Department of Pharmacology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Jalan Rungkut Madya No. 1, Surabaya, 60294, Indonesia
[b] Genetic Research Center, YARSI Research Institute, YARSI University, Jakarta Pusat, Jl. Letjen Suprapto, Cempaka Putih, 10510, Indonesia
[c] Department of Histology, Faculty of Medicine, YARSI University, Jakarta Pusat, Jl. Letjen Suprapto, Cempaka Putih, 10510, Indonesia
[d] Department of Medical Sciences, Ministry of Public Health, Tivanond Road, Nonthaburi, 11000, Thailand

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ABSTRACT

Background: The *HLA-B* alleles have been used as a marker to predict drug-induced adverse reactions and as a major contributor to hypersensitivity reactions. We examined the feasibility of *HLA-B* alleles as pharmacogenomic markers of drug-induced hypersensitivity in an Indonesian Malay Ethnic.

Methods: Fifty-eight Indonesian individuals of Malay ethnicity were enrolled in this study. *HLA-B* alleles were determined using reverse sequence-specific oligonucleotide probe coupled with xMAP technology.

Results: *HLA-B**15:02 (15.52%), *HLA-B**35:05 (9.48%), and *HLA-B**07:05 (7.76%) were frequent alleles in the Indonesian Malay ethnic populations. We discovered at least eight pharmacogenomics markers of drug-induced hypersensitivity: *HLA-B**15:02, *HLA-B**15:21, *HLA-B**13:01, *HLA-B**35:05, *HLA-B**38:02, *HLA-B**51:01, *HLA-B**57:01, and *HLA-B**58:01. *HLA-B**15:02 was in the same serotype group with *HLA-B**15:21, which is a B-75 serotype associated with genetic predisposition for carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. The Indonesian population, represented by Malay, Javanese, and Sundanese ethnicities, was similar to South East Asian, Han Chinese, and Taiwanese populations based on *HLA-B**15:02 frequency as the most common allele found in Malay ethnics.

Conclusion: We provided valuable information on the frequency of drug hypersensitivity-associated *HLA-B* alleles in Indonesian Malay ethnic population, which can improve treatment safety.

1. Introduction

The human leukocyte antigen (*HLA*) class I and II genes exhibit impressive polymorphisms and play an important role in the regulation of the immune system [1–3]. The *HLA* genes are located on chromosome 6p21.3, and the IMGT/HLA database release 3.15.0 currently contains 10.691 allele sequences [4]. Studies on the *HLA* alleles have been performed in various populations, and the results have revealed that the distribution of alleles and haplotype vary from one population to another or among members of the same ethnicity in a certain population [5–9]. Elucidating variations in the *HLA* allele will enable us to understand the development of races

* Corresponding author.
E-mail address: rika.fk@upnjatim.ac.id (R. Yuliwulandari).

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and determine the origin of different ethnic populations [6,10]. This will help unravel the evolution of humans [10].

The *HLA-B* alleles have been used as a marker to predict drug-induced adverse reactions and as a major contributor to hypersensitivity reactions involving direct stimulation of immune effector cells, simulating an allergic reaction [11]. Several studies have reported that allopurinol-induced severe cutaneous adverse reactions (SCARs) are strongly associated with the *HLA-B**58:01 allele in Han Chinese and Thais [12,13]. In addition, the *HLA-B**57:01 allele is involved in abacavir-induced hypersensitivity reaction [14]. The *HLA-B**15:02 allele is strongly related to carbamazepine-induced Steven–Johnson syndrome (SJS)-toxic epidermal necrolysis (TEN) in several Asian populations, especially in the Southeast Asian populations [15–18], including Indonesians [19]. *HLA-B* genotyping before the prescription of a medication might reduce the risk of SCARs and drug hypersensitivity reaction.

Indonesia has over 300 ethnicities, but *HLA* polymorphism in Indonesia has not been well studied. To date, there has been only one intensive *HLA* polymorphism study in Javanese and Sundanese ethnic populations [5]. The Javanese–Sundanese ethnic population is the largest ethnic population in Indonesia, especially in Java Island and our previous study showed the frequency of the *HLA-A*, *-B*, and *-DRB1* alleles and the genetic relationship between those populations and other Asian populations. The most frequent *HLA-A* alleles were *HLA-A**24:07 (21.52%), *HLA-B**15:02 (11.6%), and *DRB1**12:02 (37.8%) [5]. There are still several major ethnic populations to be investigated in relation to *HLA* polymorphism in Indonesia. It provides an opportunity to study genetic diversity, especially polymorphisms in *HLA-B,* which have been used as a marker to predict several drug hypersensitivity reactions. Therefore, we investigated *HLA-B* polymorphisms in the Indonesian Malay ethnic populations, which are large ethnic populations in Sumatra Island in Indonesia, to understand the distribution of the *HLA-B* allele to define its feasibility as a pharmacogenomics marker of adverse drug reactions.

Table 1
Human leukocyte antigen B allele frequencies in the Indonesian Malay Ethnic.

No.	Allele *HLA-B*	Frequencies	
		2n[a]	%
1	07:05	9	7.76
2	08:01	1	0.86
3	13:01	2	1.72
4	15:02	18	15.52
5	15:06	1	0.86
6	15:13	3	2.59
7	15:21	5	4.31
8	15:139	1	0.86
9	15:240	2	1.72
10	18:01	5	4.31
11	18:02	2	1.72
12	18:33	1	0.86
13	27:06	3	2.59
14	27:107	4	3.45
15	35:01	2	1.72
16	35:03	2	1.72
17	35:05	11	9.48
18	35:08	1	0.86
19	35:16	1	0.86
20	38:02	5	4.31
21	39:01	1	0.86
22	40:01	3	2.59
23	40:06	1	0.86
24	40:02	1	0.86
25	40:117	1	0.86
26	40:149	1	0.86
27	44:02	1	0.86
28	44:03	4	3.45
29	51:01	4	3.45
30	51:02	3	2.59
31	52:01	3	2.59
32	53:04	1	0.86
33	53:14	4	3.45
34	54:01	1	0.86
35	57:01	1	0.86
36	58:01	5	4.31
37	58:18	2	1.72
Total		116	100.00

Abbreviations: HLA, Human Leukocyte Antigen.
[a] 2n: the number of alleles detected in the study.

2. Methods

This study was approved by the Research Ethics Committees of the YARSI University (126/KEP-UY/BIA/VIII/2019). Samples were collected from 58 healthy individuals of Indonesian Malay ethnic. All the individuals were healthy and they provided informed consent. All subjects were interviewed for ethnic background within three generations. The subjects were included in the study if they were healthy with normal body temperature, normal blood pressure, and not receiving any treatment.

Peripheral blood samples (3 mL) were collected in EDTA tubes. DNA from peripheral blood was extracted using a QiaAmp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to manual kit instructions in YARSI Molecular Lab, YARSI Research Institute, YARSI University. The concentration of DNA was finally adjusted to 20 ng/μL and used for *HLA-B* genotyping. HLA-B genotyping was performed using a WAKFlow HLA Typing Kit (Wakunaga Pharmaceutical, Hiroshima, Japan) in molecular lab of Department of Medical Science, Ministry of Public Health, Thailand. The kit was based on the reverse sequence-specific oligonucleotide probe method coupled with xMAP technology designed for use with a Luminex 100 system (Luminex, Austin, TX). Allele frequency was calculated by direct counting. We also used the Chi-Square or Fisher exact test (when the number of tests was less than 5 to evaluate the Hardy Weinberg Equilibrium (HWE) value for our data.

3. Results

The estimated allele frequencies in the Indonesian Malay ethnic are shown in Table 1. No deviation from the Hardy–Weinberg equilibrium was observed in our samples. The most frequent allele in Malay ethnicity was *HLA-B**15:02 (15.52%). *HLA-B**15:02 is known to have a strong relationship with carbamazepine-induced SJS/TEN. Interestingly, in this study, we also found another *HLA-B* allele as a pharmacogenomics marker indicating drug-induced adverse reaction, but the frequency of this allele was small. We found in this study that the alleles *HLA-B**15:21, *HLA-B**13:01, *HLA-B**57:01, *HLA-B**58:01, *HLA-B**38:02 and *HLA-B**51:01 were related to carbamazepine-induced liver injury, dapsone-induced hypersensitivity in leprosy treatment, abacavir-induced hypersensitivity, allopurinol-induced SJS/TEN and hypersensitivity, sulfamethoxazole-induced SJS/TEN and phenytoin-induced SCAR, respectively.

The distribution of the *HLA-B* alleles that could act as pharmacogenomics markers according to ethnicity in Indonesia is indicated in Table 2. *HLA-B**15:02 was the most frequent allele found in Indonesian Malay ethnic (15.52%) and Javanese–Sundanese ethnicities (11.6%). As a pharmacogenomics marker, *HLA-B**15:02 has been studied intensively in Indonesia; its association with carbamazepine-induced SJS/TEN has attracted special attention. Therefore, we compared the frequency of *HLA-B**15:02 between Indonesian ethnic populations and different populations worldwide; the results are summarized in Table 3. The prevalence of *HLA-B* in Indonesian ethnic populations is similar to that in South East Asian populations, Han Chinese populations, and Taiwanese populations.

4. Discussion

The present study showed the distribution of the *HLA-B* allele in the Indonesian Malay ethnic populations. The Malay ethnic population is the third largest ethnic population in Indonesia and the largest ethnic population in Sumatra Island, the western part of Indonesia [20]. Herein, we describe the distribution of the *HLA-B* allele in these ethnic populations to elucidate the genetic profile of the *HLA-B* allele that have an implication in pharmacogenomics, especially in relation to drug hypersensitivity reaction.

In our study, the frequent *HLA-B* allele in the Indonesia Malay ethnic population was *HLA-B**15:02 (15.52%), followed by *HLA-B**35:05 (9.48%) and *HLA-B**07:05 (7.76%). The prevalence of the *HLA-B**15:02 allele was found to be high in South–East Asian countries. Previous studies in South–East Asian countries have shown that *HLA-B**15:02 is significantly associated with carbamazepine-induced SJS/TEN in Thailand [15], Malaysia [16], Singapore [17], and Indonesia [19]. Other Asian populations that showed a strong relationship are Indian [21], Taiwanese [22], and Han Chinese populations [23,24]. Based on the frequencies of *HLA-B**15:02, Indonesian ethnicities, represented by Malay and Javanese and Sundanese ethnicities, were similar to South East Asian, Han Chinese, and Taiwanese populations. Interestingly, in the present study, we also found *HLA-B**15:21 in the Indonesian Malay ethnic population. Some previous studies have shown that the *HLA-B**15:21 allele could also be a marker of CBZ-induced SJS/TEN [19,25,26]. *HLA-B**15:02 is in the same serotype group with *HLA-B**15:21, which is a B-75 serotype. Therefore, it was possible that patients screened negative for *HLA-B**15:02 could be positive for SJS/TEN because they have other B-serotype alleles, such as

Table 2
Distribution of *HLA-B* related to pharmacogenomics marker among Indonesian ethnicities.

HLA-B alleles	Ethnicity		
	Indonesian Malay (%)	Javanese–Sundanese (%)	Average (%)
*HLA-B**13:01	1.72	1.48	3.2
*HLA-B**15:02	15.52	11.6	13.56
*HLA-B**15:21	4.31	6.96	5.64
*HLA-B**35:05	9.48	8.44	8.96
*HLA-B**38:02	4.31	5.70	5
*HLA-B**51:01	3.45	3.16	3.31
*HLA-B**57:01	0.86	1.27	1.1
*HLA-B**58:01	4.31	5.70	5

Abbreviations: HLA, Human Leukocyte Antigen.

Table 3
Distribution of the *HLA-B**15:02 allele in different populations worldwide.

Population	Prevalence of *HLA-B**15:02	References
Indonesian Malay	15.52%	Present Study
Javanese–Sundanese	11.60%	[5]
Singapore Chinese Han	11.60%	[51]
Han Chinese	10.2%	[51]
Malay	8.4%	[51]
Thai	8.16%	[44]
Filipino (Ivatan)	22%	[51]
Taiwanese	8%	[22]
African	0.2%	[51]
Hispanic	0%	[51]
Native American	0%	[51]
Japanese	<1%	[51]
Koreans	0.5%	[51]
European Caucasians	<1%	[51]
Indians		[51]
Khandesh Pawra	6%	[51]
Mumbay Marathas	1.9%	[51]
North Hindi	2%	[51]
Bhil in Western India	4%	[51]
Punjab	1%	[51]
Parsi	0%	[51]
Tamil Nadu	1.8%	[51]

*HLA-B**15:08, *-B**15:11, *-B**15:21, and *-B**15:31 [27]. Our previous study suggests to have genetic screening for B75 serotype to predict the risk of CBZ-induced SJS/TEN more accurately than screening for a specific allele [19]. Furthermore, cost effectiveness study for *HLA-B**15:02 allele in Indonesia showed that neither *HLA-B**15:02 testing before CBZ treatment nor VPA substitution is cost-effective. However, given the improved clinical outcomes associated with the deployment of *HLA-B**15:02 genetic screening in other Asian countries, this test could be beneficial, particularly in decreasing the economic cost of CBZ-related ADRs [28,29].

We observed almost 10% of *HLA-B**35:05 allele in the Indonesian Malay ethnic. A previous study has shown that *HLA-B**35:05 is strongly associated with nevirapine-induced skin adverse reaction in Thai and Indian populations. Nevirapine is medication used to treat HIV/AIDS [30]. Another study identified *HLA-B**35:05 as a protective allele in terms of plasma viral load HIV-1 subtype A/E infection in Thailand [31]. The HIV-1 subtype A/E is a dominant subtype in Southeast Asia, especially in Myanmar, Thailand, Vietnam, Lao People's Democratic Republic, Cambodia, and Indonesia [32,33]. However, the role of *HLA-B**07:05 has not been defined, although this allele is the second-most frequent allele in the Malay population.

In this present study we found that 1.75% of the Indonesia Malay ethnic have the *HLA-B**13:01 allele. A previous study confirmed *HLA-B**13:01 as a risk factor for dapsone hypersensitivity syndrome (DHS) among patients with leprosy [34]. Dapsone is a drug used in multidrug therapy for leprosy patients besides rifampicin and clofazimine. DHS is a fatal idiosyncratic systemic hypersensitivity syndrome that can cause irreversible organ damage or even death if not recognized early and managed properly [35]. Indonesia has the third highest number of leprosy cases globally, after India and Brazil [36]. Even though we only observed small frequency in Malay people, but this information will be useful to conduct further study in dapsone-induced hypersensitivity with the Indonesia Malay ethnics leprosy patients as dapsone is still the main treatment used for leprosy. Other study also shows the specific association between *HLA-B**13:01 and dapsone-induced SCARs including SJS-TEN and DRESS in the Thai and Taiwanese population in non-leprosy patients [37]. Interestingly, recent study also showed that *HLA-B**13:01 was strongly associated with sulfamethoxazole (co-trimoxazole)-induced DRESS in Thailand and Malaysia [38]. Co-trimoxazole is known as broad-range spectrum antibiotics for various infection such as pneumonia, bronchitis, traveler's diarrhea, shigellosis, and urinary tract infections [39]. The results of those study are valuable to support the specific genotyping of the *HLA-B**13:01 allele to avoid dapsone-induced SCARs and/or sulfamethoxazole (co-trimoxazole)-induced DRESS before medication, especially in the Asian population, including in Indonesia.

*HLA-B**58:01 was reported to be associated with allopurinol-induced SJS/TEN in the Thai population [13] as well as allopurinol-induced SCARs in the Han Chinese population [12]. A case report in Javanese patients in Indonesia confirmed the association of *HLA-B**58:01 with allopurinol-induce SJS [40]. Another finding from Indonesia revealed that the *HLA-B**58 allele is a risk factor for nevirapine allergy in Indonesian HIV patients [41]. Even though there is no evidence yet of a genetic predisposition of allopurinol-induced SJS/TEN and/or SCARS in Indonesia Malay ethnic, our current study provides valuable information for *HLA-B**58:01 frequency which is comparable to other South East Asian populations including the Javanese population of Indonesia [5, 42]. Despite the region's high prevalence of *HLA-B**58:01, few Southeast Asian countries have conducted genetic screening prior to starting allopurinol treatment [43,44]. Therefore, a larger study is needed to prove a robust link between *HLA-B**58:01 and SCARs to offer evidence for policy on genetic screening tests in Indonesia.

*HLA-B**57:01 is found in small frequency in the Indonesian Malay ethnic. *HLA-B**57:01 is known to be associated with abacavir-induced hypersensitivity syndrome (AHS) [14] and it is more frequent in Caucasian populations than in Asian population [45]. Another *HLA-B* allele present in the Indonesian Malay ethnic is *HLA-B**38:02 that is associated with sulfamethoxazole-induced SJS/TEN in 28 European patients [46]. Although we only detected about 4% of *HLA-B**38:02 in this present study, a study in

Thailand discovered that *HLA-B**38:02 was significantly associated with Phenytoin induced SJS-TEN. Interestingly, the same study also reported significant association between *HLA-B**51:01 and Phenytoin induced DRESS [47]. Study by Su et al. (2019) also support these finding and revealed that *HLA-B**51:01 was significantly associated with phenytoin hypersensitivity in East Asian population [48]. Other studies in China have showed that the presence of *HLA-B**38:02 is associated with the risk of Carbimazole/Methimazole induce agranulocytosis in antithyroid medication [49]. All above information is important for Indonesian Malay ethnic as baseline data to conduct case control study to get predisposition genetic evidence.

To the best of our knowledge, our study is the first to report *HLA-B* polymorphism in the Indonesian Malay ethnic. However, our study has some limitations. First, the small sample size of in the present study might have affected the frequency estimates in the loci studied. There was a chance of missing an allele with a small sample size. Second, the SSO method requires the preparation of specific oligonucleotides corresponding to various genotypes in advance and potential difficulties may arise when new rare alleles are present. The results obtained by the SSO method are in medium resolution; in some cases, different alleles share similar sequences across the sequenced region, leading to ambiguity in allele determination and requiring careful analysis and review [2]. Therefore, to overcome this issue, further testing is required by other high-resolution methods, such as Sanger-based typing or next generation sequencing [50]. However, this should bear little significance to our findings, as this study was the first attempt to show the diversity of *HLA-B* alleles in the Indonesian Malay ethnic. *HLA*-associated drug hypersensitivity is ethnicity-specific and differs among populations studied, based on variations in genetic backgrounds.

5. Conclusion

Our findings suggested that screening for *HLA-B* genotype, especially for pharmacogenomics marker alleles, such as *HLA-B**15:02, *HLA-B**15:21, *HLA-B**13:01, *HLA-B**35:05, *HLA-B**38:02, *HLA-B**51:01, *HLA-B**57:01 and *HLA-B**58:01, and should be conducted before administration of drugs to reduce the incidence of drug hypersensitivity. Our study provided useful information for further studies on pharmacogenomics and *HLA-B* polymorphisms in the Indonesian population. Knowledge on the frequency of the *HLA-B* alleles associated with drug hypersensitivity can improve treatment safety. Our findings might facilitate the development and implementation of genetic screening tests that are affordable and easy to use in clinical practice and accelerate the implementation of personalized medicine through pharmacogenomics study in Indonesia. Preclinical research focusing on specific interactions between *HLA-B* alleles and drugs can be carried out to identify strategies to develop safer drugs.

Ethics declaration

This study was approved by the Research Ethics Committees of the YARSI University (No. 126/KEP-UY/BIA/VIII/2019). All subjects had signed written informed consent.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

CRediT authorship contribution statement

Rika Yuliwulandari: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization. **Kinasih Prayuni:** Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Data curation. **Kencono Viyati:** Writing – original draft, Resources, Methodology, Formal analysis. **Surakameth Mahasirimongkol:** Writing – review & editing, Visualization, Data curation, Conceptualization. **Nuanjun Wichukchinda:** Writing – review & editing, Visualization, Validation, Software, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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