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# Association of the HLA-B alleles with carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis in the Javanese and Sundanese population of Indonesia: the important role of the HLA-B75 serotype

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Carbamazepine (CBZ) is a common cause of life-threatening cutaneous adverse drug reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Previous studies have reported a strong association between the HLA genotype and CBZ-induced SJS/TEN. We investigated the association between the HLA genotype and CBZ-induced SJS/TEN in Javanese and Sundanese patients in Indonesia. Nine unrelated patients with CBZ-induced SJS/TEN and 236 healthy Javanese and Sundanese controls were genotyped for HLA-B and their allele frequencies were compared. The *HLA-B\*15:02* allele was found in 66.7% of the patients with CBZ-induced SJS/TEN, but only in 29.4% of tolerant control ( $p = 0.029$ ; odds ratio [OR]: 6.5; 95% CI: 1.2–33.57) and 22.9% of healthy controls ( $p = 0.0021$ ; OR: 6.78; 95% CI: 1.96–23.38). These findings support the involvement of *HLA-B\*15:02* in CBZ-induced SJS/TEN reported in other Asian populations. Interestingly, we also observed the presence of the *HLA-B\*15:21* allele. *HLA-B\*15:02* and *HLA-B\*15:21* are members of the HLA-B75 serotype, for which a greater frequency was observed in CBZ-induced SJS/TEN (vs tolerant control [ $p = 0.0078$ ; OR: 12; 95% CI: 1.90–75.72] and vs normal control [ $p = 0.0018$ ; OR: 8.56; 95% CI: 1.83–40]). Our findings suggest that screening for the HLA-B75 serotype can predict the risk of CBZ-induced SJS/TEN more accurately than screening for a specific allele.

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**Keywords:** carbamazepine • HLA-B75 • Indonesia • Javanese • Stevens–Johnson syndrome • Sundanese • toxic epidermal necrolysis

Carbamazepine (CBZ) is used to treat seizures, neuropathic pain such as trigeminal neuralgia, chronic pain and bipolar disorder [1,2]. CBZ is effective in most patients and is usually recommended as the first line antiepileptic. Additionally, it is available as a generic medication and thus is generally affordable [3]. Previous studies have shown that CBZ is a common cause of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [4–6].

SJS/TEN is characterized by erythematous skin, extensive detachment of the epidermis and erosion of the mucous membranes; it is a single-disease entity which is present at different severities but with a common pathogenesis [7]. SJS/TEN patients are classified based on the extent of skin detachment: limited to less than 10% of the body surface area (BSA) in SJS, 10–30% BSA in SJS/TEN overlap, and more than 30% of the BSA in TEN [1,7].

Multiple studies have shown the association between HLA genotype and CBZ-induced SJS/TEN [8]; some HLA alleles have been reported to be strong predictive markers for SJS/TEN [9]. The most prominent marker reported for CBZ-induced SJS/TEN is *HLA-B\*15:02*, which is commonly found in southeast Asian populations [2,5,10–16], while other studied populations were found to lack a correlation between the *HLA-B\*15:02* genotype and SJS/TEN risk [17–19]. This indicates that the *HLA-B\*15:02* allele is not a universal marker for CBZ-induced SJS/TEN risk, but instead may vary by ethnicity [17,20]. A recent study reported the case of a Thai patient who developed CBZ-induced SJS while screening negative for *HLA-B\*15:02*, but was later found to have *HLA-B\*15:21* [21]; other HLA-B75 serotype markers similar to *HLA-B\*15:02* are *HLA-B\*15:08*, *-B\*15:11* and *-B\*15:31* [22].

A previous study of HLA in the Javanese and Sundanese populations of Indonesia showed an *HLA-B\*15:02* allele frequency of 11.6% [23]. Because of the relatively high frequency of the *HLA-B\*15:02* allele in these populations, it is important to determine the association between *HLA-B\*15:02* and CBZ-induced SJS/TEN among the Javanese and Sundanese ethnic groups. Therefore, in this study, we investigated the association between the *HLA-B\*15:02* genotype and the B-75(15) serotype and CBZ-induced SJS/TEN in Javanese and Sundanese populations. To the best of our knowledge, this report constitutes the first study of the genetic associations of drug-induced SJS/TEN in these populations.

## Materials & methods

Genetic samples from 12 patients of Javanese and Sundanese ethnicity with CBZ-induced SJS/TEN were collected during 2014–2015 from several hospitals on Java Island. Patients were diagnosed according to Roujeau's diagnostics criteria and confirmed by dermatologist based on the clinical morphology of their skin damage [24]. The CBZ-tolerant control group of Javanese or Sundanese ethnicity consisted of 17 patients with epilepsy who did not show any cutaneous reaction 3 months after taking CBZ. Samples from 236 unrelated healthy individuals of Javanese or Sundanese ethnicity in the general population were obtained as part of a previous study [25] and used as normal controls. All subjects were interviewed for ethnic background for three generations back. The genomic DNA for both groups was isolated in the same manner and stored at  $-20^{\circ}\text{C}$  until further processing. The study protocols were approved by the Research Ethics Committees of YARSI University, Jakarta, Indonesia and YARSI collaborative hospitals, and all subjects signed informed consent forms.

HLA-B genotypes were determined using a Luminex multianalyte profiling system (xMAP; Luminex, TX, USA) with a WAKFlow HLA typing kit (Wakunaga, Hiroshima, Japan), which is based on polymerase chain reaction-reverse sequence-specific oligonucleotide probes, according to the manufacturer's instructions. The HLA alleles were assigned by analyzing hybridization patterns of the target using WAKFlow HLA typing software (Wakunaga).

HLA-B genotype and HLA-B75 serotype frequencies were compared between patients and controls using  $\chi^2$  test. The strength of association was estimated by calculating the odds ratio (OR) and 95% CI. All reported p-values were two-sided, and a value of  $p < 0.05$  was considered statistically significant. The HLA-B75 serotype was defined using the IMGT/HLA database nomenclature [22].

## Results

12 patients with CBZ-induced SJS/TEN and 17 tolerant controls were recruited in this study. General population control from previous study was also included in analysis to search for an association between HLA allele and CBZ-induced SJS/TEN. All alleles with frequencies  $<1\%$  in the general population control groups were classified as B others (Table 1). Most of the subjects were female (53%) and the median age was 34.25 years old (15–59 years old). The presence of *HLA-B\*15:02* in CBZ-induced SJS/TEN (8/12; 66.7%) was significantly more than that of the CBZ-tolerant control group (4/17; 29.4%;  $p = 0.029$ ; OR: 6.5; 95% CI: 1.2–33.57) and than that of normal controls (54/236; 22.9%;  $p = 0.0021$ ; OR: 6.78; 95% CI: 1.96–23.38), see Table 1. The *HLA-B\*18:01* allele tended to occur more often in patients, but statistical significance was not reached (33.3% [3/9] in SJS/TEN patients compared with 5.9% in tolerant control and 12.3% in general population controls). *HLA-B\*44:03* and *HLA-B\*15:21* allele frequencies were also higher in patients, but not statistically significant (Table 1). Table 2 shows the association between the HLA-B75 serotype and CBZ-induced SJS/TEN. The presence of HLA-B75 serotype was higher in CBZ-induced SJS/TEN patients (10/12; 83.3%) than in tolerant control (5/17; 29.4%)

Table 1. Frequencies of heterogenous alleles of HLA-B loci.

HLA-B allele	Frequency (%)			Case with SJS/TEN vs general control		Case with SJS/TEN vs tolerant control	
	SJS/TEN (n = 12)	General control (n = 236) <sup>†</sup>	Tolerant control (n = 17)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
07:02	–	4 (1.7%)	–	–	–	–	–
07:05	–	12 (5.1%)	2 (11.8%)	–	–	–	–
13:01	–	6 (2.5%)	–	–	–	–	–
13:02	–	5 (2.1%)	–	–	–	–	–
15:02	8 (66.7%)	54 (22.9%)	4 (29.4%)	6.78 (1.96–23.38)	0.0021	6.5 (1.2–33.57)	0.029
15:12	–	6 (2.5%)	–	–	–	–	–
15:13	–	51 (21.6%)	2 (11.8%)	–	–	–	–
15:17	–	4 (1.7%)	–	–	–	–	–
15:21	2 (16.7%)	33 (14%)	1 (5.9%)	1.24 (0.26–5.89)	1	3.2 (0.26–40.05)	0.55
15:214	1 (8.3%)	–	1 (5.9%)	–	–	–	–
15:25	–	8 (3.4%)	–	–	–	–	–
15:32	–	4 (1.7%)	–	–	–	–	–
18:01	4 (33.3%)	29 (12.3%)	1 (5.9%)	3.59 (1.02–12.66)	0.06	8 (0.76–83.88)	0.12
18:02	–	8 (3.4%)	2 (11.8%)	–	–	–	–
18:33	–	–	1 (5.9%)	–	–	–	–
27:06	–	14 (5.9%)	–	–	–	–	–
35:01	–	–	2 (11.8%)	–	–	–	–
35:02	–	–	1 (5.9%)	–	–	–	–
35:03	–	11 (4.7%)	–	–	–	–	–
35:05	1 (8.3%)	39 (16.5%)	4 (23.5%)	0.42 (0.053–3.36)	0.49	0.29 (0.02–3.04)	0.37
35:32	1 (8.3%)	–	–	–	–	–	–
38:02	–	25 (10.6%)	–	–	–	–	–
40:01	–	17 (7.2%)	1 (5.9%)	–	–	–	–
40:06	–	4 (1.7%)	–	–	–	–	–
44:03	3 (25%)	42 (17.8%)	5 (29.4%)	0.46 (0.58–3.68)	0.7	0.8 (0.15–4.26)	1
44:13	1 (8.3%)	–	–	–	–	–	–
51:01	–	15 (6.4%)	2 (11.8%)	–	–	–	–
51:02	–	16 (6.8%)	–	–	–	–	–
52:01	–	5 (2.1%)	–	–	–	–	–
52:02	–	–	2 (11.8%)	–	–	–	–
56:02	–	4 (1.7%)	–	–	–	–	–
57:01	–	6 (2.5%)	–	–	–	–	–
58:01	–	27 (11.4%)	–	–	–	–	–
B others	–	15 (6.4%)	–	–	–	–	–

<sup>†</sup>From Javanese and Sundanese General Population [25].

"–" no data available.

SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis.

Table 2. HLA-B75 serotype carrier frequency in carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis patients and normal controls.

HLA-B serotype	Frequency (%)			Case with SJS/TEN vs general control		Case with SJS/TEN vs tolerant control	
	SJS/TEN (n = 12)	General control (n = 236)	Tolerant control (n = 17)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
B75	10 (83.3%)	87 (36.9%)	5 (29.4%)	8.56 (1.83–40)	0.0018	12 (1.90–75.72)	0.0078

SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis.

and general population control (87/236; 36.9%). It was revealed that HLA-B75 allele is significantly associated with CBZ-induced SJS/TEN compared with tolerant control ( $p = 0.0078$ ; OR: 12; 95% CI: 1.90–75.72) and general population control ( $p = 0.0018$ ; OR: 8.56; 95% CI: 1.83–40).

## Discussion

We determined the HLA-B genotypes in 12 CBZ-induced SJS/TEN patients, 17 CBZ-tolerant patients and 236 normal controls using a high-resolution DNA typing method. We found that *HLA-B\*15:02* was the most frequent allele, and observed a strong association between the *HLA-B\*15:02* allele and the risk of CBZ-induced SJS/TEN in Javanese and Sundanese populations. These findings are similar to those of other studies in Asian populations [2,5,10–16]. However, there are some reported cases of patients who developed CBZ-induced SJS while screening negative for *HLA-B\*15:02*. Kaniwa *et al.* [19] reported not detecting *HLA-B\*15:02* in Japanese SJS/TEN patients receiving CBZ, instead finding *HLA-B\*15:11*, which belongs to the same HLA-B75 serotype. Mehta *et al.* [16] investigated the association between *HLA-B\*15:02* and CBZ-induced SJS in eight Indian patients. While they found that six of the patients did carry *HLA-B\*15:02*, one patient was homozygous *HLA-B\*15:08*. Tassaneeyakul *et al.* (2010) [26] detected *HLA-B\*15:21* and *HLA-B\*15:11* in a Thai population with CBZ-induced SJS/TEN.

We also identified *HLA-B\*15:21* in patients who screened negative for *HLA-B\*15:02* but developed SJS/TEN (Table 1). Despite the lack of statistical significance, most likely because of the small patient sample, the finding of *HLA-B\*15:21* in our study could indicate possible CBZ-induced SJS/TEN in patients who screen negative for *HLA-B\*15:02*, especially in the Javanese and Sundanese ethnicities. This suggests that CBZ-induced SJS/TEN may be serotype-specific. However, in this study, we only detected the *HLA-B\*15:02* and *HLA-B\*15:21* alleles. A recent study from Jaruthamsophon *et al.* [21] reported a positive association between *HLA-B\*15:21* and CBZ-induced SJS/TEN in Asian populations.

Interestingly, in this study, we also found *HLA-B\*18:01* and *HLA-B\*44:03*; both are members of the HLA B44 supertype, the most frequent serotype in our study, and share a peptide-binding specificity [27,28]. Sidney *et al.* reported that some peptides derived from hepatitis B and C viruses, HIV and *Plasmodium falciparum* have degenerative B44 supertype-binding capacity [28].

In developing a risk assessment strategy to prevent CBZ-induced SJS/TEN in Indonesia, it would be necessary to take into account the increased likelihood that B75 serotype alleles contribute to the condition. Further work should be conducted to characterize the role of *HLA-B\*15:21* in CBZ-induced SJS/TEN, by expanding this study to other populations. Our findings showed that the HLA-B75 serotype was strongly associated with CBZ-induced SJS/TEN, and was a stronger predictor than *HLA-B\*15:02* alone. We suggest that Asians with the HLA-B75 serotype should be considered at-risk for CBZ-induced SJS/TEN, and not only individuals carrying the *HLA-B\*15:02* allele. Hence, it would be beneficial to develop a diagnostic kit for estimating the risk for CBZ-induced SJS/TEN, especially in Asian populations.

The current study is limited by its small sample size, resulting in a wide CI. Nonetheless, further research is warranted to identify drugs which may induce SJS/TEN, as well as other HLA alleles that can predispose specific populations to SJS/TEN. In conclusion, we have been able to establish an association between the HLA-B75 serotype and CBZ-induced SJS/TEN that is stronger than the well-established association of CBZ-induced SJS/TEN with *HLA-B\*15:02*, in Javanese and Sundanese patients in Indonesia. Our study provides primary evidence that the development of public health recommendations and efficient assays for HLA-75 serotype screening would benefit the cohort under consideration.

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## Financial & competing interests disclosure

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## Summary points

- Carbamazepine (CBZ) is common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN).
- *HLA-B\*15:02* is a well-known genetic marker for CBZ-induced SJS/TEN in Southeast–Asian population.

## Materials &amp; methods

- A total 12 patients of CBZ-induced SJS/TEN, 17 patients of CBZ-tolerant SJS/TEN and unrelated 236 healthy control of Javanese or Sundanese ethnicity were involved in this study.
- HLA-B genotypes were determined using a Luminex multianalyte profiling system (xMAP) with a WAKFlow HLA typing kit (Wakunaga), which is based on polymerase chain reaction-reverse sequence-specific oligonucleotide probes.

## Results

- Our result supports the role of *HLA-B\*15:02* in CBZ-induced SJS/TEN that was reported in other Asian population.
- We found that *HLA-B\*15:02* and *HLA-B\*15:21*, classified as HLA B-75 serotype, related to CBZ-induced SJS/TEN in Indonesian population.

## Conclusion

- We found significant association between B-75 serotype and CBZ-induced SJS/TEN.
- Screening of HLA-B75 serotype is suggested to prevent SJS/TEN in Southeast–Asian population, instead of *HLA-B\*15:02* only.

No writing assistance was utilized in the production of this manuscript.

## Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigators. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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