

CORRESPONDENCE

Association between *HLA-B*15:02* and carbamazepine induced severe cutaneous adverse drug reactions in Myanmar

Genetic predisposition to carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) had been reported in several Southeast Asian populations, but not in Myanmar. Previous studies had so far reported more than 70% of CBZ-induced SJS/TEN cases positive for *HLA-B*15:02* allele.¹⁻⁴ Myanmar, as the second largest country in Southeast Asia with a population of 54.5 million, has high *HLA-B*15:02* carrier frequency in its general population (27.3-49.1%).^{5,6} We investigated the association of HLA-B alleles and CBZ-induced SJS/TEN in Myanmar population. *HLA-B*15:02* was detected in 3/3 (100%) of cases and 6/53 (11.3%) of tolerant controls, and *HLA-B*15:02* is significantly associated with CBZ-SJS/TEN in Myanmar population (OR 51.2, 95% CI 2.36-1106.95, $p=0.003$).

Patients with CBZ-SJS and carbamazepine-tolerant controls were recruited from Yangon General Hospital, Myanmar (2014-2015). This study was approved by Yangon General Hospital ethics committee (No: 09/2014). Written informed consent was obtained prior to participation. The diagnosis of SJS was made by dermatologists based on diagnostic criteria by Roujeau JC *et al.* and Batsuji *et al.*^{7,8} The causal relationship between CBZ and SJS was determined based on ALDEN score of 6 and above. Exposure was based on the latent time between starting drug treatment and index day of adverse cutaneous reactions. CBZ-tolerant controls were patients on CBZ for at least 3 months without hypersensitivity reactions. Patient's medication history, dosage, concurrent drugs and history of allergy were recorded. Six ml of venous blood sample was obtained from each patient for HLA genotyping.

For HLA-B allele genotyping, DNA was extracted from blood samples with QiaAmp DNA kit (Qiagen, Hilden, Germany). HLA-B allele genotyping was performed with WAKFlow HLA typing kit (Wakunaga Pharmaceutical Co. Ltd, Japan) and analysed by Luminex 200 (Luminex, Austin, TX, USA).

HLA-B carrier frequencies between groups were compared with Fisher's exact test. All P -value is two-tailed and $p<0.05$ indicated statistical significance. Odds ratio (OR) and 95% confidence interval (CI) was obtained through contingency table and Haldane's modification was used to counter for zero count cells.

Demographic data of CBZ-SJS case and CBZ-tolerant controls were presented in Table 1. Our cohort comprised of 3 CBZ-SJS patients and 53 CBZ-tolerant controls. All CBZ-SJS cases was female with mean age of 31.3 years. In CBZ-tolerant control group, gender distribution was equal.

The mean time latency between starting CBZ and index-day was 23.3 ± 11.5 days. There was no significant difference between the CBZ average daily dose in cases (mean, 366.7mg/d) and tolerant controls (mean, 580.8mg/d) ($P=0.29$) (Table 1).

Association analysis was performed for 3 CBZ-SJS cases and 53 CBZ-tolerant controls. *HLA-B*15:02* was detected in 3/3 (100%) of cases and 6/53 (11.3%) of tolerant controls ($P=0.003$, OR 51.2, 95% CI 2.36-1106.95). The sensitivity and specificity of the *HLA-B*15:02* test in CBZ-SJS/TEN of Myanmar origin were 100% and 88.7% respectively. Some of the common alleles found in the tolerant control groups were *HLA-B*52:01* (26.4%), *B*44:03* (15.1%) and *B*38:02* (13.2%).

Thus, in this study, we detected significant association between *HLA-B*15:02* and CBZ-SJS in Myanmar population with *HLA-B*15:02* presence in all cases. This is consistent with previous studies reporting on neighbouring populations where the risk allele is common (4-17.7%).^{3-5,9,10}

Table 1: Demographic and clinical characteristic of patients with CBZ-induced SJS/TEN and CBZ tolerant controls

	CBZ-SJS/TEN (n=3)	CBZ Tolerant Controls (n=53)	P-value
Sex, n (%)			
Female	3 (100%)	26 (49.1%)	
Male	0 (0%)	27 (50.9%)	
Age (years), mean (range)	31.3 (18-51)	27.4 (12-63)	0.57
CBZ exposure			
Dosage, mean (range), mg/d	366.7 (200-600)	580.8 (200-1800)	0.29
Duration, mean \pm SD (range), d	23.3 \pm 11.5 (10-30)	NA	

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; CBZ, Carbamazepine; SD, standard deviation; d, day; mg, miligram

Diversity studies on HLA-B*15 allele subtype in Myanmar population showed *HLA-B*15:02* as the most common allele in Bamar (8.8%) and Karen (12.4%) ethnic groups. Bamar is the largest ethnic group (68%) in Myanmar, who are of Sino-Tibetan origin migrated from western China and China-India borderlands.^{11,12} The study further compared HLA-B*15 distribution to neighbouring population of Vietnamese, Thais and Han Chinese noting the similar frequency.⁶ Recently Nguyen *et al.* reported the association of *HLA-B*15:02* and CBZ-SJS/TEN in Vietnamese.³ This study showed that Myanmar population is similar to other populations in Southeast Asia, with *HLA-B*15:02* being a strong predisposing factor in CBZ-SJS/TEN.

Our study is limited in the number of CBZ-SJS/TEN cases due to rare incidence. To further validate this association, future study with a larger number of samples is required.

In conclusion, this study demonstrated that *HLA-B*15:02* is significantly associated with CBZ-SJS/TEN in Myanmar population. Therefore, Myanmar population with considerably high frequency of *HLA-B*15:02* have an increased risk of developing CBZ-SJS/TEN in carriers of *HLA-B*15:02*. Taking into account that *HLA-B*15:02* test is estimated to be 80-97% sensitive and 81-97% specific in populations where the risk variant is common (more than 5% in general population), it is therefore advisable for people of Myanmar to have *HLA-B*15:02* screening prior to commencing CBZ treatment.

^{1,2}Amy Hui-Ping Khor, ³Seinn Mya Mya Aye, ¹Kheng-Seang Lim, ³Yan Lynn Aung, ³Yin Minn Aye, ³Ohnmar, ³Win Min Thit, ¹Chong-Tin Tan, ²Ching-Ching Ng

¹Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya; ²Genetics and Molecular Biology Unit, Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia; ³Department of Neurology, Yangon General Hospital, Yangon, Myanmar

Address correspondence to: Dr Kheng-Seang Lim, Neurology Laboratory, 6th floor, Menara Selatan, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia. Tel: +60-14-7214303, E-mail: kslimum@gmail.com

Keywords: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Carbamazepine, *HLA-B*15:02*, Myanmar

Financial support: This study is funded by University of Malaya under High Impact Research from Ministry of Higher Education research funds (reference no.: UM.C/625/1/HIR/MOHE/CHAN-02 and reference no.: UM.C/625/1/HIR/MOHE/MED/45)) and Postgraduate Research Fund (grant no.: PG112-2015B).

Conflict of Interest: None

REFERENCES

1. Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfirevic A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. *Clin Pharmacol Ther* 2012; 92(6):757-65.
2. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, *et al.* Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia* 2010; 51(5):926-30.
3. Nguyen DV, Chu HC, Nguyen DV, *et al.* HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pacific Allergy* 2015; 5(2):68-77.
4. Kosama H, Budikayanti A, Khor AHP, *et al.* HLA-B*1502 and carbamazepine induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Indonesia. *Neurol Asia* 2017; 22(2):113-6.
5. Gonzalez-Galarza FF, Takeshita LY, Santos EJ, *et al.* Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res* 2015; 43(Database issue):D784-8.
6. Kongmaroeng C, Romphruk A, Puapairoj C, *et al.* HLA alleles and haplotypes in Burmese (Myanmarese) and Karen in Thailand. *Tissue Antigens* 2015; 86(3):199-204.
7. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; 129(1):92-6.
8. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; 331(19):1272-85.
9. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol* 2013; 149(9):1025-32.
10. Khor AH, Lim KS, Tan CT, *et al.* HLA-A*31: 01 and HLA-B*15:02 association with Stevens-Johnson syndrome and toxic epidermal necrolysis to carbamazepine in a multiethnic Malaysian population. *Pharmacogenetics Genomics* 2017; 27(7):275-8.
11. Introduction to Myanmar, Ministry of Foreign Affairs, Republic of the Union of Myanmar. Republic of the Union of Myanmar; Available from: http://www.mofa.gov.mm/?page_id=12.
12. Naing UM, Thant H. National ethnic groups of Myanmar: Daw Moe Kay Khaing; 2000.