ความสัมพันธ์ระหว่างปัจจัยทางพันธุกรรมและปัจจัยที่ไม่เกี่ยวข้องกับพันธุกรรมกับการเกิดอาการไม่พึงประสงค์ทางผิวหนังจากยาคาร์บามาเซปินในผู้ป่วยชาวไทย
Associations of Genetic and Non-genetic Factors with Carbamazepine-induced Cutaneous Adverse Drug Reactions in Thai Patients

นิพนธ์ต้นฉบับ **Original Article**

ฐาปนัท นาคครุฑ[1], ชลภัทร สุขเกษม[2] และ ศราวุฒิ อู่พุฒินันท์[3]*

[1] ฝ่ายเภสัชกรรม สถาบันประสาทวิทยา เขตทุ่งพญาไท กรุงเทพฯ 10400
[2] ห้องปฏิบัติการเภสัชพันธุ์ศาสตร์และการแพทย์เฉพาะบุคคล คณะแพทย์ศาสตร์ โรงพยาบาลรามาธิบดี เขตทุ่งพญาไท กรุงเทพฯ 10400
[3] ภาควิชาเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์ มหาวิทยาลัยนเรศวร อ.เมือง จ.พิษณุโลก 65000

* Corresponding author: sarawuto@nu.ac.th

วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2565;17(4):352-359.

Thapanat Nakkrut[1]*, Chonlaphat Sukasem[2] and Sarawut Oo-puthinan[3]*

[1] Department of Pharmacy, the Neurological Institute of Thailand, Phayathai, Bangkok, 10400, Thailand
[2] Laboratory for Pharmacogenomics and Personalized Medicine, Faculty of Medicine, Ramathibodi Hospital, Phayathai, Bangkok, 10400, Thailand
[3] Department of Pharmacy Practice, Faculty of Pharmacy, Naresuan University, Mueang, Phitsanulok, 65000, Thailand

* Corresponding author: sarawuto@nu.ac.th

Thai Pharmaceutical and Health Science Journal 2022;17(4):352-359.

บทคัดย่อ

วัตถุประสงค์ เพื่อทดสอบความสัมพันธ์ระหว่างยีน HLA class I รวมทั้งปัจจัยที่ไม่เกี่ยวข้องกับพันธุกรรมกับการเกิดผื่นแพ้ยาชนิด SJS/TEN และ MPE จากยาคาร์บามาเซปินในผู้ป่วยชาวไทย **วิธีการศึกษา** เป็นการศึกษาแบบควบคุมกลุ่มโดยการสังเกตแบบย้อนหลัง จากผู้ป่วยชาวไทยที่มีประวัติการได้รับยาคาร์บามาเซปินที่สถาบันประสาทวิทยา ระหว่าง พ.ศ. 2550 - 2560 มีอาสาสมัครเข้าร่วมกลุ่มเคสทั้งหมด 89 คน แบ่งเป็นผู้ที่เกิดผื่นแพ้ยาชนิด SJS/TEN 16 คน และชนิด MPE 22 คน และอาสาสมัครกลุ่มควบคุมซึ่งไม่เกิดผื่นแพ้ยา 51 คน ทบทวนประวัติของอาสาสมัครและตรวจวิเคราะห์หาลักษณะทางพันธุกรรม ทดสอบความสัมพันธ์ระหว่าง HLA class I และปัจจัยอื่น ๆ กับการเกิดผื่นแพ้ยาด้วยการทดสอบความถดถอยแบบโลจิสติก **ผลการศึกษา** พบว่าอัลลีล *HLA-B*15:02* (OR = 14; *P*-value < 0.001; 95%CI = 3.66 - 53.53) และ *HLA-A*02:03* (OR = 5.46; *P*-value = 0.022; 95%CI = 1.30 - 22.80) สัมพันธ์กับการเกิดผื่นแพ้ยาชนิด SJS/TEN จากยาคาร์บามาเซปิน และอัลลีล *HLA-B*51:01* (OR = 4.71; *P*-value = 0.049; 95%CI = 1.01 - 21.83) สัมพันธ์กับการเกิดผื่นแพ้ยาชนิด MPE ไม่พบว่าปัจจัยที่ไม่เกี่ยวข้องกับพันธุกรรม ได้แก่ อายุ ขนาดยา การใช้ยาที่อาจทำให้เกิดอันตรกิริยาระหว่างร่วมด้วย หรือประวัติการแพ้ยาสัมพันธ์กับการเกิดผื่นแพ้ยาจากยาคาร์บามาเซปินในทั้งสองแบบ **สรุป:** ยีน *HLA class I* สัมพันธ์กับการเกิดผื่นแพ้ยาชนิด SJS/TEN และ MPE จากยาคาร์บามาเซปิน โดยพบว่า *HLA-B*15:02* และ *HLA-A*02:03* สัมพันธ์กับการเกิด SJS/TEN และ *HLA-B*51:01* นั้นสัมพันธ์กับการเกิด MPE ส่วนปัจจัยที่ไม่เกี่ยวข้องกับพันธุกรรมต้องมีการศึกษาเพิ่มเติมโดยใช้ผู้ป่วยจำนวนมากกว่านี้

คำสำคัญ: HLA, Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular eruption, คาร์บามาเซปิน

Editorial note
Manuscript received in original form: March 16, 2022;
Revision notified: April 19, 2022;
Revision completed: May 19, 2022;
Accepted in final form: June 18, 2022;
Published online: December 31, 2022.

Abstract

Objective: To investigate the association of HLA class I and non-genetic factors with carbamazepine (CBZ)-induced SJS/TEN and MPE in Thai patients. **Methods:** This was a retrospective case-control study in Thai patients who had previously received carbamazepine at Neurological Institute of Thailand between 2007 and 2017. With a total of 89 participants, 16 and 22 were with SJS/TEN and MPE (or cases), respectively, and 51 were CBZ-tolerant (controls). The medical records were reviewed and genetic markers were analyzed. Associations between the HLA class I and various factors with the adverse reactions were tested using logistic regression. **Result:** There were significant associations between *HLA-B*15:02* (OR = 14; *P*-value < 0.001; 95%CI = 3.66 - 53.53) and *HLA-A*02:03* (OR = 5.46; *P*-value = 0.022; 95%CI = 1.30 - 22.80). *HLA-B*51:01* was associated with CBZ-induced MPE (OR = 4.71; *P*-value = 0.049; 95%CI = 1.01 - 21.83). No no-genetic factors (i.e., age, dose, concurrent potential interacting drugs and history of drug allergy) were associated with CBZ-induced cADRs. **Conclusion:** The HLA class I gene was associated with SJS/TEN and MPE rash from carbamazepine. *HLA-B*15:02* and *HLA-A*02:03* were associated with SJS/TEN and *HLA-B*51:01* was associated with MPE. The associations of non-genetic factors and CBZ-induced cADRs need to be answered in future studies with more power.

Keywords: HLA, Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular eruption, carbamazepine

Journal website: http://ejournals.swu.ac.th/index.php/pharm/index

Introduction

Carbamazepine (CBZ) is an anti-epileptic drug for focal seizures and generalized seizures with a long history of use. It has been one of the most used anti-epileptic drugs. In Thailand, CBZ is in the category A in the National Essential Drug List 2020. In all levels of healthcare settings in Thailand, it is considered a standard drug for epilepsy with its obvious clinical evidence and long-standing clinical experience in treating epilepsy, neuropathic pain, and mania. Since CBZ is effective and less costly, it is selected as the first choice of in epilepsy and neuropathic pain such as trigeminal neuralgia. For bipolar disorder, even though CBZ is not the first choice, it has been used for patients unable to use the first-line drugs, for example, those allergic to such drugs[1] and those under 13

years of age which is contra-indicated for lithium. CBZ is also recommended in neuropathic pain.

CBZ asserts its effect through inhibiting voltage-gated sodium channel. It is metabolized mainly by CYP3A4 into carbamazepine-10,11-epoxide which is an active metabolite. This epoxide metabolite has been reported to be toxic to central nervous system and its related adverse effects.[2] The most frequently found side effects of CBZ include dizziness, vertigo, and nausea. About 3 – 5% of the patients experience hypersensitivity to CBZ with the symptoms ranging from urticaria to Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN) which is life-threatening.[3] One-year mortality rate of TEN is 34%. Among those experiencing TEN who survived, long-term effects including permanent body scars, visual loss, and chronic kidney disease.[4] For maculopapular eruption (MPE), a non-severe from of cutaneous adverse drug reaction, it has been associated with a high incidence of 1.7/100,000 when compared with that of SJS/TEN (0.1/100,000).[5] A high incidence rate of CBZ-related MPE is of a great concern, but studies on genetic factors on CBZ-related MPE in Thai patients have been limited.[6-12]

Human Leukocyte Antigen (HLA) is located on the short arm of human chromosome 6. HLA helps code for proteins that differentiate between self and non-self which is critical in the immune system. With its genetic diversity, genetic expressions of HLA vary immensely among different individuals. HLA is categorized into 3 classes (i.e., HLA class I, II and III) with differences in size and function. HLA class I has a size of 2,000 kb and is found on the cell with nucleus. HLA class I that presents antigens found in the cell to CD^+8 cytotoxic T lymphocyte includes HLA-A, HLA-B and HLA-C. Previous studies revealed the associations between *HLA-B*15:02* alleles and SJS/TEN cutaneous reactions of CBZ. The study of Grover and colleagues found that HLA-B*1502 allele is associated with SJS/TEN cutaneous reactions of CBZ with an odds ratio (OR) of 80.70.[6] However, studies on the associations between *HLA-B*15:02* allele and CBZ-related MPE have been scarce. Four studies in Han Chineses in China, *HLA-B*15:02* allele was not associated with CBZ-related MPE[7-10]; while one of Hung and co-workers found that *HLA-A*31:01* allele was associated with CBZ-related MPE (OR = 17.5; 95% CI = 4.6 – 66.5; p-value = 0.0022).[10] In Thailand, a study showed that *HLA-B*15:02* allele was not associated with MPE.[11] For *HLA-A*31:01* allele, the study of Amstutz and colleagues in 2013 in diverse Canadian ethnicities revealed that CBZ-relate MPE was associated with the allele (OR = 8.57; 95% CI = 1.67 – 57.50; p-value = 0.0037).[12] Studies on CBZ cutaneous reactions in association with HLA alleles other than *HLA-B*15:02* have been scarce and their sample sizes were relatively limited.[13] In Thailand, no studies on HLA alleles other than *HLA-B*15:02* and CBZ cutaneous reactions have been found.

For non-genetic factors, studies suggest reproductive women have a higher risk of anti-epileptic drugs than men.[14] Other factors relating to anti-epileptic drugs include age, co-morbid illnesses, and concomitant drugs with potential drug interaction.[15] Patients allergic to anti-epileptic drugs have a higher chance of being allergic to other drugs than those who are not. Patients allergic to other anti-epileptic drugs are 9.3 times more likely to be allergic to CBZ than those never allergic to any anti-epileptic drugs.[16] Based on the findings from previous studies, there is a need to determine the genetic association of HLA class I alleles both HLA-A and HLA-B with CBZ-related cutaneous drug reactions including the severe SJS/TEN and MPE types in Thai patients. Laboratory test for HLA gene could help avoid CBZ allergy.

Specifically, this study aimed to determine the association of genetic factor (i.e., HLA-A and HLA-B alleles) and non-genetic factors with the incidence of carbamazepine-induced SJS/TEN and MPE in Thai patients.

Methods

In this retrospective case-control study, participants were patients treated with carbamazepine at the Neurological Institute of Thailand, Bangkok, between January 2007 and December 2017. Inclusion criteria for cases and controls were based on the study of Askmark and colleagues.[17] To be eligible, they had to have Thai nationality and be treated with carbamazepine. For **cases** or those with the adverse events, they had to be diagnosed with CBZ-related MPE or SJS/TEN within 3 months since the start of CBZ. For controls or CBZ-tolerant patients, they had to use CBZ continuously for at least 6 months and had no CBZ-related MPE or SJS/TEN. Participants who were excluded were those with unclear treatment history, younger than 20 years, with psychiatric problems, unable to communicate in Thai language either by reading or writing, or unwilling to participate. HLA genotypes both in cases with CBZ-related MPE or SJS/TEN and CBZ-tolerant controls were determined by blood test.

Cutaneous Adverse Drug Reactions(cADR) was defined as any skin hypersensitivity reactions regardless of severity, i.e, from mild to life-threatening ones. For **general control** group, they were Thai individuals with no history of drug allergies. This group consisted of 470 individuals of general Thai population with *HLA-A* and *HLA-B* alleles data.[18]

Data collection

Demographic and clinical characteristics of the participants were extracted from medical records. These included gender, age, history of drug allergy and exposure of CBZ. For **cases**, exposure of CBZ was defined as dose and duration of CBZ use till the incident of cADRs. For **CBZ-tolerant controls**, it was the CBZ use till the discontinuation date of CBZ with reasons other than allergy including acceptable disease control and medication change, otherwise till the data collection date. Concomitant drugs were also extracted from medical records. These drugs included clarithromycin, diltiazem, fluoxetine, quetiapine, verapamil, levetiracetam, and valproate sodium. Drug allergy signs and or symptoms were also extracted. These included date of the incident, type of rash, affected area, mucosal involvement Details also included the inflammation of cutaneous membranes (i.e., mouth, eyes, and genital area), gastrointestinal symptoms, respiratory symptoms, and other symptoms. Laboratory investigation measures (i.e., CBC and liver functions) at the hospitalization date or ER visit date were extracted to confirm the allergy. Duration since the start of CBZ until the allergy, physician diagnosis (type of rash and causative drugs), and HLA class I alleles genotypes (i.e., HLA-A and HLA-B alleles) were also extracted.

HLA Class I allele variation determination

HLA Class I allele variation was determined as follows.

1. Buffy coat was prepared by sampling 10 mL of blood sample stored in the EDTA tube to be centrifuged at 2500 rpm and temperature 25 ˚C for 15 minutes. The buffy coat was drawn and stored at -20 ˚C until DNA extraction.

2. DNA was extracted using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) and stored at -20 ˚C until HLA Class I allele variation determination.

3. In HLA Class I allele variation determination, the DNA extract was diluted to the final concentration of 30 µg/mL. HLA Class I allele variation was determined by the polymerase chain reaction and sequence specific oligonucleotide probes (PCR-SSOP) using Luminex commercial HLA genotyping kit and the HLA genotypes were analyzed by the software program HLA Fusion 2.0. Samples of participants with MPE and SJS/TEN were analyzed separately.

Data analysis

Descriptive statistics including mean with standard deviation and frequency with percentage were used to present demographic and clinical characteristics of the participants. For univariate analysis, differences in categorical variables among the three groups of cutaneous adverse reactions (i.e., SJS/TEN cases, MPE cases, and CBZ-tolerant controls) were tested with chi-square test or Fisher's exact test as appropriate. Differences in continuous variables among the three groups were tested with ANOVA or Kruskal-Wallis test as appropriate. Any of these non-genetic factors that were found significantly associated with the incident of any of cutaneous adverse reactions were also controlled for in the logistic regression analysis.

In logistic regression analysis, the associations between having CBZ-associated SJS/TEN and different HLA class I genotypes and non-genetic factors were tested for CBZ-tolerant controls. The associations between having CBZ-associated MPE and HLA class I genotypes and non-genetic factors were also tested in a similar fashion. Similar associations were also tested with general controls without non-genetic factors. The associations were presented as odds ratio (OR) with 95% confidence interval. Statistical significance for all statistical tests was set at a type I error of 5% (or P-value < 0.05). Statistical analyses were performed using statistical software program SPSS version 25.

Participant protection

The study was approved by the Ethics Committee for Human Study of Naresuan University (approval number: 566/2018; approval date: September 30, 2018). Participants were informed about the objective, process, and voluntary and anonymity nature of the study.

Results

Based on records of potential participants which were patients receiving care from January 2007 to December 2017, cutaneous adverse drug reactions (cADRs) of patients while using CBZ were 23 cases of SJS or TEN and 31 cases of MPE. Of these potential participants, 16 patients with

SJS/TEN and 22 patients with MPE were willing to participate in the study as cases when contacted. In addition, 51 patients with no allergy to CBZ were willing to participate in the study as CBZ-tolerant controls. All 89 patients provided their written informed consent. For general Thai population controls, a sample of 470 individuals with data of *HLA-A* and *HLA-B* alleles genotypes was successfully secured for analysis.

It was found that patients with SJS/TEN, MPE and no adverse reactions were not different regarding gender where women were found 62.5%, 68.2%, and 49.0%, respectively (*P*-value = 0.278). Mean ages in the three groups were comparable (46.38 ± 13.83, 49.00 ± 15.69, and 47.23 ± 18.88 years, respectively, *P*-value 0.873). Median daily doses of CBZ were also comparable (400, 300, and 400 mg/day, respectively, *P*-value = 0.070), with the lowest and highest doses of 100 and 1,600 mg/day, respectively.

For the duration of CBZ use, CBZ-tolerant controls used carbamazepine for at least 182 days (or 6 months) with no cADRs (i.e., the use till the discontinuation date of CBZ with reasons other than allergy including acceptable disease control and medication change, otherwise till the data collection date for CBZ-tolerant controls). For those SJS/TEN cases and MPE cases, their median times to experience the cADRs were relatively comparable with 15 and 20 days, respectively, and the ranges of 5 – 60 and 14 – 90 days, respectively. In brief, cases had the shorter medians than those CBZ-tolerant controls. This suggests that the data were valid since patients with allergy usually experience the event at the early use of the causative drug. It was found that 13.6% of those with MPE and 11.8% of those with no cADRs used drugs with potential interaction with CBZ, while none of those with SJS/TEN did so. This difference was also not significant (*P*-value = 0.348).

Since all non-genetic factors were not significantly associated with the incident of any cADRs, they were not controlled for in the analysis of risk of cADRs with HLA alleles in the following section. For the duration of carbamazepine use till the incident of cADRs (days), since it merely reflected the nature, not the cause of the association, it was not tested in the further logistic regression.

Table 1 Demographic and clinical characteristics of cases and controls (N = 89).

Characteristics	N (%)			*P*-value*
	SJS/TEN cases (n = 16)	MPE cases (n = 22)	CBZ-tolerant controls (n = 51)	
Gender				
Men	6 (37.5)	7 (31.8)	26 (51.0)	0.278§
Women	10 (62.5)	15 (68.2)	25 (49.0)	
Age (years)				
Mean ± SD	46.38 ± 14.83	49.00 ± 15.69	47.23 ± 18.88	0.873#
Carbamazepine daily dose (mg/day)				
Median	400	300	400	0.070‡
Range	100 - 400	100 – 1,200	100 – 1,600	
Duration of carbamazepine use till the incident of cADRs (days)$				
Median	15	20	480	< 0.001†
Range	5 - 60	14 - 90	182 - 3,285	
Use of drugs with potential interaction with carbamazepine				
Yes	0 (0)	3 (13.6)	6 (11.8)	0.348§
No	16 (100.0)	19 (86.4)	45 (88.2)	
Drugs allergy history				
No allergy	16 (100)	21 (95)	43 (84)	0.548§
Aromatic AEDs	0 (0)	1 (5)	5 (10)	
Other drugs	0 (0)	0 (0)	3 (6)	

* Comparisons between SJS/TEN, MPE, and control groups, unless stated otherwise.
§ Fisher's exact test (two-tailed). # ANOVA.
‡ Kruskal-Wallis test. † Mann-Whitney U test between SJS/TEN and MPE groups.
$ Duration of carbamazepine use till the incident of ADR for cases, or till the discontinuation date of CBZ with reasons other than allergy including acceptable disease control and medication change, otherwise till the data collection date for CBZ-tolerant controls.

Among 89 patients with SJS/TEN (n = 16), MPE (n = 22) and no cADRs (n = 51), a total of 41 alleles, specifically 16 HLA-A alleles and 25 HLA-B alleles, were found (Table 2). *HLA-A*02:03* was the most frequently found HLA-A allele in patients with SJS/TEN (35.00%) (Table 2). *HLA-A*02:03* was significantly associated with a 5- to 6-fold risk of CBZ-related SJS/TEN when compared with those without the allele, specifically with ORs of 5.455 and 5.621 when compared with CBZ-tolerant controls and general population controls, respectively (Table 3). For HLA-B, *HLA-B*15:02* was the most found allele (40.62%) (Table 2). *HLA-B*15:02* was significantly associated with a 14- to 17-fold risk of CBZ-related SJS/TEN when compared with those without the allele, specifically with ORs of 14.000 and 16.859 when compared with CBZ-tolerant controls and general population controls, respectively (Table 3).

For MPE, the most found allele was *HLA-B*58:01* (18.18%), followed by *HLA-B*15:02, HLA-B*40:01, HLA-B*51:01* (11.36% each) (Table 2). Further logistic regression analysis revealed that only *HLA-B*51:01* was significantly associated with a 3- to 4-fold risk of CBZ-related MPE when compared with those without the allele, specifically with ORs of 4.706 and 3.162 when compared with CBZ-tolerant controls and general population controls, respectively (Table 3).

Table 2 Frequencies of HLA-A and HLA-B alleles found in patients with SJS/TEN and MPE associated with carbamazepine and in carbamazepine-tolerant controls (N = 89).

HLA alleles		N of alleles (%)			
		SJS/TEN cases	MPE cases	CBZ-tolerant controls	Total
HLA-A		**(2n = 20)**	**(2n = 36)**	**(2n = 102)**	**(2n = 158)**
HLA-A total	*HLA-A*01:01*	-	1 (2.78)	1 (0.98)	2 (1.26)
	*HLA-A*02:01*	2 (10.00)	2 (5.56)	6 (5.88)	10 (6.33)
	*HLA-A*02:03*	7 (35.00)	5 (13.89)	11 (10.78)	23 (14.56)
	*HLA-A*02:06*	1 (5.00)	1 (2.78)	3 (2.94)	5 (3.16)
	*HLA-A*02:07*	-	2 (5.56)	7 (6.86)	9 (5.70)
	*HLA-A*11:01*	4 (20.00)	9 (25)	28 (27.45)	41 (25.95)
	*HLA-A*11:02*	-	1 (2.78)	-	1 (0.63)
	*HLA-A*11:04*	-	1 (2.78)	-	1 (0.63)
	*HLA-A*24:02*	4 (20.00)	3 (8.33)	15 (14.70)	22 (13.92)
	*HLA-A*24:10*	1 (5.00)	-	2 (1.96)	3 (1.90)
	*HLA-A*29:01*	-	1 (2.78)	1 (0.98)	2 (1.26)
	*HLA-A*33:01*	1 (5.00)	2 (5.56)	-	3 (1.90)
	*HLA-A*33:03*	-	5 (13.89)	9 (8.82)	14 (8.86)
	*HLA-A*34:01*	-	1 (2.78)	4 (3.92)	5 (3.16)
	*HLA-A*68:01*	-	1 (2.78)	1 (0.98)	2 (1.26)
	*HLA-A*74:01*	-	1 (2.78)	1 (0.98)	2 (1.26)
HLA-B		**(2n = 32)**	**(2n = 44)**	**(2n = 102)**	**(2n = 176)**
HLA-B total	*HLA-B*07:05*	2 (6.25)	1 (2.27)	3 (2.94)	6 (3.41)
	*HLA-B*08:01*	-	1 (2.27)	-	1 (0.57)
	*HLA-B*13:01*	1 (3.12)	-	7 (6.86)	8 (4.54)
	*HLA-B*13:02*	-	1 (2.27)	1 (0.98)	2 (1.14)
	*HLA-B*15:01*	1 (3.12)	-	1 (0.98)	2 (1.14)
	*HLA-B*15:02*	13 (40.62)	5 (11.36)	8 (7.84)	26 (14.77)
	*HLA-B*15:21*	2 (6.25)	-	1 (0.98)	3 (1.70)
	*HLA-B*18:01*	2 (6.25)	3 (6.81)	3 (2.94)	8 (4.54)
	*HLA-B*18:02*	1 (3.12)	-	1 (0.98)	2 (1.14)
	*HLA-B*18:15*	-	2 (4.54)	-	2 (1.14)
	*HLA-B*27:04*	-	2 (4.54)	2 (1.96)	4 (2.27)
	*HLA-B*27:06*	-	1 (2.27)	2 (1.96)	3 (1.70)
	*HLA-B*33:09*	1 (3.12)	-	-	1 (0.57)
	*HLA-B*35:03*	1 (3.12)	-	1 (0.98)	2 (1.14)
	*HLA-B*40:01*	-	5 (11.36)	7 (6.86)	12 (6.82)
	*HLA-B*40:02*	-	1 (2.27)	-	1 (0.57)
	*HLA-B*44:03*	1 (3.12)	2 (4.54)	3 (2.94)	6 (3.41)
	*HLA-B*46:01*	5 (15.62)	3 (6.81)	16 (15.69)	24 (13.64)
	*HLA-B*51:01*	-	5 (11.36)	2 (1.96)	7 (3.78)
	*HLA-B*51:02*	-	1 (2.27)	-	1 (0.57)
	*HLA-B*54:01*	-	1 (2.27)	-	1 (0.57)
	*HLA-B*55:01*	-	1 (2.27)	1 (0.98)	2 (1.14)
	*HLA-B*56:04*	1 (3.12)	-	1 (0.98)	2 (1.14)
	*HLA-B*57:01*	-	1 (2.27)	3 (2.94)	4 (2.27)
	*HLA-B*58:01*	1 (3.12)	8 (18.18)	6 (5.88)	15 (8.52)

Discussions and Conclusion

Our findings indicated that patients with *HLA-B*15:02* and *HLA-A*02:03* alleles were associated with a higher risk of carbamazepine-induced cutaneous adverse reactions specifically SJS or TEN compared with those without the alleles. The association of *HLA-B*15:02* with the risk of carbamazepine-induced SJS/TEN is consistent with previous studies. The study of Chung and colleagues revealed a 2,504-fold risk of SJS/TEN among Han Chineses with *HLA-B*15:02* allele compared with those without the allele.[19]

Such association of *HLA-B*15:02* allele and SJS/TEN among patients taking carbamazepine was reported in many studies not only in Han Chineses[10, 20-29], but also Thais[30-32], Indians[33-35], Vietnameses[36], Malaysian[37], Spanish[38], Javaneses/ Sudaneses in Indonesia[39], and others.[40,41] The strength of the association in our study with an OR of 14.00 is lower than those in previous studies in Thais. This low strength of the association could be in part due to a smaller number of patients with *HLA-B*15:02* allele of 12 out of 16 (75.00%) which is lower than 88 – 100% found in previous studies in Thai patients.[30-32]

For *HLA-A*02:03* allele, it was found for the first time in this study to be associated with SJS/TEN with carbamazepine. The risk of SJS/TEN among patients with *HLA-A*02:03* was 5 times of that in those without the allele. It was found that 35.00% of patients with SJS/TEN had the allele, while 10.78% of those CBZ-tolerant controls and 13.92% of general Thai population controls did so. There have been no studies showing the association between *HLA-A*02:03* and cADR.[42] More studies should be conducted to prove such association of *HLA-A*02:03* and SJS/TEN with carbamazepine.

For MPE caused by carbamazepine, studies in Europeans and Canadians found that *HLA-A*31:01* allele was associated with a 5 to 8-fold risk of MPE.[40,43,44] However, in Han Chineses, the results on such association were conflicting.[10,24,43] In this present study, no *HLA-A*31:01* was found either in patients with MPE or those CBZ-tolerant controls. Certain studies showed the association of *HLA-A*31:01* allele with MPE caused by carbamazepine in Chineses[10], Europeans[43,44], Japaneses[45], and ethnicity-diversed Canadians.[40] But there are no previous studies to show such association in Thais which are consistent with this present study.

For *HLA-B*51:01* allele, it was found to be associated with a higher risk MPE with an OR of 4.7. *HLA-B*51:01* allele was overtly presented in patients with MPE (11.36%), and much less in CBZ-tolerant controls (1.96%) and general Thai population controls (4.54%). The study of Likkasittipan and colleagues revealed that *HLA-B*51:01* allele was associated with cutaneous adverse reactions caused by phenobarbital in Thai children.[46] As high as 50% of the patients experiencing cutaneous adverse reactions had *HLA-B*51:01* allele; while only 6% of those without the reaction did so. They reported a 15-fold risk of MPE with the presence of *HLA-B*51:01* allele.[46]

Table 3 Associations between HLA-A and HLA-B genotypes and incidence of cADRs related to carbamazepine.*

ปัจจัยทางพันธุกรรม		Carrier			Cases vs CBZ-tolerant controls			Cases vs General Thai population		
		Cases	CBZ-tolerant controls	General Thai population	*P*-value	OR	95% CI	*P*-value	OR	95% CI
SJS/TEN		**(n = 10)**	**(n = 51)**	**(n = 470)**						
	*HLA-A*02:01*	2 (20%)	6 (11.76%)	51 (10.85%)	0.607	1.875	0.320 - 10.988	0.304	2.054	0.425 - 9.937
	*HLA-A*02:03*	6 (60%)	11 (21.57%)	99 (21.06%)	0.022*	5.455	1.305 - 22.801	0.009*	5.621	1.556 - 20.307
	*HLA-A*02:06*	1 (10%)	3 (5.88%)	21 (4.47%)	0.521	1.778	0.166 - 19.065	0.377	2.376	0.287 - 19.631
	*HLA-A*11:01*	4 (40%)	23 (45.10%)	211 (44.89%)	1.000	0.812	0.204 - 3.227	1.000	0.818	0.228 - 2.938
	*HLA-A*24:02*	3 (30%)	13 (25.49%)	95 (20.21%)	0.713	1.253	0.282 - 5.569	0.434	1.692	0.429 - 6.665
HLA-A	*HLA-A*24:10*	1 (10%)	2 (3.92%)	16 (3.40%)	0.421	2.722	0.223 - 33.279	0.305	3.153	0.376 - 26.405
Total	*HLA-A*33:01*	1 (10%)	0	3 (0.64%)	0.164	NA	NA	0.81	17.296	1.637 - 182.696
		(n = 16)	**(n = 51)**	**(n = 470)**						
	*HLA-B*07:05*	2 (12.5%)	3 (5.88%)	24 (5.11%)	0.586	2.286	0.347-15.064	0.209	2.655	0.571 - 12.352
	*HLA-B*13:01*	1 (6.25%)	7 (13.72%)	54 (11.49%)	0.669	0.419	0.048-3.691	1.000	0.514	0.067 - 3.966
	*HLA-B*15:01*	1 (6.25%)	1 (1.96%)	5 (1.06%)	0.423	3.333	0.196-56.554	0.183	6.200	0.682 - 56.390
	*HLA-B*15:02*	12 (75%)	9 (17.65%)	71 (15.11%)	0.000	14.000	3.661-53.53	0.000	16.859	5.2388 - 53.748
	*HLA-B*15:21*	2 (12.5%)	1 (1.96%)	2 (0.42%)	0.139	7.143	0.603 - 84.660	0.006	33.429	4.387 - 254.726
	*HLA-B*18:01*	2 (12.5%)	3 (5.88%)	36 (7.66%)	0.586	2.286	0.347 - 15.064	0.360	1.722	0.377 - 7.875
	*HLA-B*18:02*	1 (6.25%)	1 (1.96%)	15 (3.19%)	0.423	3.333	0.196 - 56.554	0.420	2.022	0.250 - 16.326
	*HLA-B*33:09*	1 (6.25%)	0	0	0.239	NA	NA	0.033	NA	NA
HLA-B	*HLA-B*35:03*	1 (6.25%)	1 (1.96%)	7 (1.49%)	0.423	3.333	0.196 - 56.554	0.236	4.410	0.510 - 38.139
Total	*HLA-B*44:03*	1 (6.25%)	3 (5.88%)	42 (8.94%)	1.000	1.067	0.103 - 11.032	1.000	0.679	0.088 - 5.271
	*HLA-B*46:01*	5 (31.25%)	14 (27.45%)	122 (25.96%)	0.760	1.201	0.354 - 4.081	0.576	1.297	0.442 - 3.807
	*HLA-B*56:04*	1 (6.25%)	1 (1.96%)	12 (2.55%)	0.423	3.333	0.196 - 56.554	0.356	2.544	0.310 - 20.858
	*HLA-B*58:01*	1 (6.25%)	6 (11.76%)	57 (12.13%)	1.000	0.500	0.056 - 4.495	0.707	0.483	0.063 - 3.726
MPE		**(n = 18)**	**(n = 51)**	**(n = 470)**						
	*HLA-A*01:01*	1 (5.56%)	1 (1.96%)	21 (4.5%)	0.457	2.941	0.174 - 49.636	0.571	1.258	0.160 - 9.905
	*HLA-A*02:01*	2 (11.11%)	6 (11.76%)	51 (11%)	1.000	0.938	0.171 - 5.126	1.000	1.027	0.230 - 4.595
	*HLA-A*02:03*	5 (27.78%)	11 (21.57%)	99 (21%)	0.746	1.399	0.409 - 4.777	0.556	1.441	0.502 - 4.139
	*HLA-A*02:06*	1 (5.56%)	3 (5.88%)	21 (4.5%)	1.000	0.941	0.092 - 9.671	0.571	1.258	0.160 - 9.905
	*HLA-A*02:07*	2 (11.11%)	7 (13.72%)	68 (14%)	1.000	0.786	0.148 - 4.184	1.000	0.739	0.166 - 3.286
	*HLA-A*11:01*	8 (44.44%)	23 (45.10%)	211 (45%)	0.002*	0.974	0.330 - 2.871	0.001	0.982	0.381 - 2.532
	*HLA-A*11:02*	1 (5.56%)	0	17 (3.6%)	0.261	NA	NA	0.498	1.567	0.197 - 12.473
HLA-A	*HLA-A*11:04*	1 (5.56%)	0	5 (1%)	0.261	NA	NA	0.203	5.471	0.606 - 49.417
Total	*HLA-A*24:02*	2 (11.11%)	13 (25.49%)	95 (20%)	0.321	0.365	0.074 - 1.808	0.547	0.493	0.112 - 2.183
	*HLA-A*29:01*	1 (5.56%)	1 (1.96%)	5 (1%)	0.457	2.941	0.174 - 49.636	0.203	5.471	0.606 - 49.417
	*HLA-A*33:01*	1 (5.56%)	0	3 (0.6%)	NA	NA	NA	0.140	9.157	0.905 - 92.651
	*HLA-A*33:03*	5 (27.78%)	9 (17.65%)	99 (21%)	0.496	1.795	0.510 - 6.314	0.556	1.441	0.502 - 4.139
	*HLA-A*34:01*	1 (5.56%)	3 (5.88%)	9 (2%)	1.00	0.941	0.092 - 9.671	0.316	3.013	0.361 - 25.151
	*HLA-A*68:01*	1 (5.56%)	1 (1.96%)	9 (2%)	0.457	2.941	0.174 - 49.636	0.316	3.013	0.361 - 25.151
	*HLA-A*74:01*	1 (5.56%)	1 (1.96%)	6 (1.3%)	0.457	2.941	0.174 - 49.636	0.233	4.549	0.519 - 39.906
		(n = 22)	**(n = 51)**	**(n = 470)**						
	*HLA-B*07:05*	1 (4.5%)	3 (5.88%)	24 (5%)	1.000	0.762	0.075 - 7.757	1.000	0.885	0.114 - 6.858
	*HLA-B*08:01*	1 (4.5%)	0	3 (0.6%)	0.301	NA	NA	0.168	7.413	0.739 - 74.307
	*HLA-B*13:02*	1 (4.5%)	1 (1.96%)	20 (4%)	0.515	2.381	0.142 - 39.876	1.000	1.071	0.137 - 8.368
	*HLA-B*15:02*	5 (23%)	9 (17.65%)	71 (15%)	0.747	1.373	0.401 - 4.695	0.361	1.653	0.591 - 4.623
	*HLA-B*18:01*	2 (9.1%)	3 (5.88%)	36 (7.6%)	0.634	1.600	0.248 - 10.316	0.684	1.206	0.271 - 5.364
	*HLA-B*18:15*	2 (9.1%)	0	0	0.088	NA	NA	0.02	NA	NA
	*HLA-B*27:04*	2 (9.1%)	2 (3.92%)	19 (4%)	0.579	2.450	0.322 - 18.613	0.240	2.374	0.571 - 10.900
	*HLA-B*27:06*	1 (4.5%)	2 (3.92%)	12 (2.6%)	1.000	1.167	0.100 - 13.578	0.452	1.817	0.226 - 14.641
HLA-B	*HLA-B*40:01*	5 (23%)	7 (13.72%)	58 (12%)	0.492	1.849	0.516 - 6.628	0.183	2.089	0.743 - 5.877
Total	*HLA-B*40:02*	1 (4.5%)	0	7 (1.5%)	0.301	NA	NA	0.308	3.150	0.370 - 26.782
	*HLA-B*44:03*	2 (9.1%)	3 (5.88%)	42 (8.9%)	0.634	1.600	0.248 - 10.316	1.000	1.019	0.230 - 4.511
	*HLA-B*46:01*	3 (14%)	14 (27.45%)	122 (26%)	1.642	0.417	0.107 - 1.633	1.683	0.450	0.131 - 1.549
	*HLA-B*51:01*	5 (23%)	3 (5.88%)	40 (8.5%)	0.049*	4.706	1.014 - 21.831	0.041*	3.162	1.108 - 9.021
	*HLA-B*51:02*	1 (4.5%)	0	13 (2.8%)	0.301	NA	NA	0.478	1.674	0.209 - 13.406
	*HLA-B*54:01*	1 (4.5%)	0	8 (1.7%)	0.301	NA	NA	0.340	2.750	0.329 - 23.011
	*HLA-B*55:01*	1 (4.5%)	1 (1.96%)	1 (0.2%)	0.515	2.381	0.142 - 39.876	0.088	22.333	1.350 - 369.500
	*HLA-B*57:01*	1 (4.5%)	3 (5.88%)	11 (2.3%)	1.000	0.762	0.075 - 7.757	0.426	1.987	0.245 - 16.118
	*HLA-B*58:01*	7 (32%)	6 (11.76%)	57 (12%)	0.051	3.500	1.016 - 12.060	0.016	3.381	1.322 - 8.647

* Logistic regression analysis on the incident of cADRs in association with HLA alleles; no non-genetic factors were controlled for since they were not significantly associated with the incident of any cADRs in univariate analyses.

In addition, the study in South Koreans of Kim and co-workers showed that 3 out of SJS/TEN cases had *HLA-B*51:01* (60.00%).[47] Such association of *HLA-B*51:01* with SJS/TEN was not found in our present study.

Our results showed no association of incident of cutaneous adverse reactions and non-genetic factors either age, dose, concomitant drugs with interaction potentials, or history of drug allergy. However, it is inconclusive whether any of these non-genetic factors are related to the risk of cutaneous adverse reactions. Since the sample size in this single-center study was relatively small, power for the statistical test could be expectedly low.

In addition to *HLA-B*15:02*, this present study found *HLA-A*02:03* and *HLA-B*51:01* alleles were also associated with a higher risk of SJS/TEN caused by carbamazepine in Thais.

These two alleles could be added to the target genes screening to prevent carbamazepine allergy and optimize the treatment.

In conclusion, *HLA-A*02:03* and *HLA-B*15:02* alleles were significantly positively associated with carbamazepine-induced SJS/TEN while *HLA-B*51:01* allele was significantly positively associated with carbamazepine-induced MPE. No non-genetic factors were associated with either carbamazepine-induced SJS/TEN or MPE.

References

1. Committee for National Essential Drugs List. National Essential Drugs List 2021. Royal Thai Government Gazette 2021;May 31, 2021: pp. 1,24,27,28.
2. Gierbolini J, Giarratano M, Benbadis SR. Carbamazepine-related antiepileptic drugs for the treatment of epilepsy - a comparative review. *Expert Opin Pharmacother* 2016;17(7):885-888.
3. Błaszczyk B, Lasoń W, Czuczwar SJ. Antiepileptic drugs and adverse skin reactions: An update. *Pharmacol Rep* 2015;67(3):426-434.
4. Yip VLM, Pirmohamed M. The HLA-A*31:01 allele: influence on carbamazepine treatment. *Pharmacogenomics Pers Med* 2017;10:29-38.
5. Fowler T, Bansal AS, Lozsádi D. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure* 2019;72:61-70.
6. Grover S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. *Pharmacogenet Genomics* 2014;24(2):94-112.
7. Wu XT, Hu FY, An DM, et al. Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. *Epilepsy Behav* 2010;19(3):405-408.
8. Wang Q, Zhou J-q, Zhou L-m, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. *Seizure* 2011;20(6):446-448.
9. Liao W-P, Shi Y, Cheng S, Ng M, Kwan P (eds.). Association between HLA-B* 1502 allele and cutaneous reactions induced by carbamazepine or lamotrigine in Han Chinese. *Epilepsia* 2009;50:252-253.
10. Hung S-I, Chung W-H, Jee S-H, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16(4):297-306.
11. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;49(12):2087-2091.
12. Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia* 2014;55(4): 496-506.
13. Striano P, Zara F. HLA alleles linked to carbamazepine hypersensitivity. *Nat Rev Neurol* 2011;7:365-366.
14. Alvestad S, Lydersen S, Brodtkorb E. Rash from antiepileptic drugs: influence by gender, age, and learning disability. *Epilepsia* 2007;48(7): 1360-1365.
15. Ye Y-M, Thong BY-H, Park H-S. Hypersensitivity to antiepileptic drugs. *Immunol Allergy Clin North Am* 2014;34(3):633-643.
16. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007;68(20): 1701-1709.
17. Askmark H, Wiholm BE. Epidemiology of adverse reactions to carbamazepine as seen in a spontaneous reporting system. *Acta Neurol Scand* 1990;81(2):131-140.
18. Satapornpong P, Jinda P, Jantararoungtong T, et al. Genetic diversity of HLA class I and class II alleles in Thai populations: contribution to genotype-guided therapeutics. *Front Pharmacol* 2020;11:article78:22 pgs.
19. Chung W-H, Hung S-I, Hong H-S, et al. A marker for Stevens–Johnson syndrome. *Nature* 2004;428(6982):486.
20. Cheung YK, Cheng SH, Chan EJ, Lo SV, Ng MH, Kwan P. HLA‐B alleles associated with severe cutaneous reactions to antiepileptic drugs in H an C hinese. *Epilepsia* 2013;54(7):1307-1314.
21. He X-J, Jian L-Y, He X-L, et al. Association between the HLA-B* 15: 02 allele and carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han individuals of northeastern *China. Pharmacol Rep* 2013;65(5):1256-1262.
22. Shi Y-W, Min F-L, Zhou D, et al. HLA-A* 24: 02 as a common risk factor for antiepileptic drug–induced cutaneous adverse reactions. *Neurology* 2017;88(23):2183-2191.
23. Wang W, Hu F-Y, Wu X-T, An D-M, Yan B, Zhou D. Genetic predictors of Stevens–Johnson syndrome and toxic epidermal necrolysis induced by aromatic antiepileptic drugs among the Chinese Han population. *Epilepsy Behav* 2014;37:16-19.
24. Hsiao Y-H, Hui RC-Y, Wu T, et al. Genotype–phenotype association between HLA and carbamazepine-induced hypersensitivity reactions: strength and clinical correlations. *J Dermatol Sci* 2014;73(2):101-109.
25. Genin E, Chen D, Hung S, et al. HLA-A* 31: 01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. *Pharmacogenomics J* 2014; 14(3):281-288.
26. Zhang Y, Wang J, Zhao L-M, et al. Strong association between HLA-B* 1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. *Eur J Clin Pharmacol* 2011;67(9):885-887.
27. Wu X, Hu F, An D, et al. Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B* 1502 allele among patients in central China. *Epilepsy Behav* 2010;19(3):405-408.
28. Wang Q, Zhou J-q, Zhou L-m, et al. Association between HLA-B* 1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. *Seizure* 2011;20(6):446-448.
29. Shi YW, Min FL, Qin B, et al. Association between HLA and Stevens–Johnson syndrome induced by carbamazepine in Southern Han Chinese: genetic markers besides B* 1502? *Basic Clin Pharmacol Toxicol* 2012;111(1):58-64.
30. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens‐Johnson syndrome is associated with HLA‐B* 1502 allele in Thai population. *Epilepsia* 2008;49(12):2087-2091.
31. 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):926-930.

32. Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, et al. HLA‐B* 1502 strongly predicts carbamazepine‐induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Thai patients with neuropathic pain. *Pain Pract* 2012;12(3):202-208.
33. Mehta TY, Prajapati LM, Mittal B, et al. Association of HLA-B* 1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. *Indian J Dermatol Venereol Leprol* 2009;75(6):579-582.
34. Aggarwal R, Sharma M, Modi M, kumar Garg V, Salaria M. HLA-B* 1502 is associated with carbamazepine induced Stevens–Johnson syndrome in North Indian population. *Hum Immunol* 2014;75(11):1120-1122.
35. Khor AHP, Lim KS, Tan CT, Wong SM, Ng CC. HLA‐B* 15:02 association with carbamazepine‐induced Stevens‐Johnson syndrome and toxic epidermal necrolysis in an I ndian population: a pooled‐data analysis and meta-analysis. *Epilepsia* 2014;55(11):e120-e124.
36. Nguyen DV, Chu HC, Nguyen DV, et al. HLA-B* 1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac Allergy* 2015;5(2):68-77.
37. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA‐B* 1502 allele with carbamazepine‐induced toxic epidermal necrolysis and Stevens–Johnson syndrome in the multi‐ethnic Malaysian population. *Int J Dermatol* 2011;50(2):221-224.
38. Ramírez E, Bellón T, Tong HY, et al. Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population. *Pharmacol Res* 2017;115:168-178.
39. Yuliwulandari R, Kristin E, Prayuni K, et al. 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. *Pharmacogenomics* 2017;18(18):1643-1648.
40. Amstutz U, Ross CJ, Castro‐Pastrana LI, et al. HLA‐A* 31: 01 and HLA‐B* 15: 02 as genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther* 2013;94(1):142-149.
41. Chong KW, Chan DW, Cheung YB, et al. Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B* 1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore. *Arch Dis Child* 2014;99(6):581-584.
42. Kloypan C, Koomdee N, Satapornpong P, Tempark T, Biswas M, Sukasem C. A comprehensive review of HLA and severe cutaneous adverse drug reactions: Implication for clinical pharmacogenomics and precision medicine. *Pharmaceuticals* 2021;14(11):article 1077:34 pages.
43. McCormack M, Gui H, Ingason A, et al. Genetic variation in CFH predicts phenytoin-induced maculopapular exanthema in European-descent patients. *Neurology* 2018;90(4):e332-e341.
44. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A* 3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 2011;364(12):1134-1143.
45. Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies HLA-A* 3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 2011; 20(5):1034-1041.
46. Likkasittipan P, Manuyakorn W, Mahasirimongkol S, et al. The association of HLA-B* 5101 and phenobarbital-induced severe cutaneous adverse drug reactions in Thai children. *J Allergy Clin Immunol* 2015;135(2):AB115.
47. Kim E, Ghim J, Jung H, Parvez M, Kim J, Shin J. HLA-B* 5101 Aalele and lamotrigine-induced Stevens-Johnson sydrome in Korean. *Clin Ther* 2015;37(8):e88. (doi: https://doi.org/10.1016/j.clinthera.2015.05.255).