Original Investigation

Relationship Between the *HLA-B*1502* Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

A Systematic Review and Meta-analysis

Wimonchat Tangamornsuksan, PharmD; Nathorn Chaiyakunapruk, PharmD, PhD; Ratchadaporn Somkrua, PharmD; Manupat Lohitnavy, PhD; Wichittra Tassaneeyakul, PhD

IMPORTANCE The US Food and Drug Administration recommends screening for the *HLA-B*1502* allele before initiation of carbamazepine therapy in patients of Asian ancestry, but there remains unclear evidence of a relationship between *HLA-B*1502* and Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) among carbamazepine users, especially in some racial/ethnic populations.

OBJECTIVE To determine the relationship between the *HLA-B*1502* allele and carbamazepine-induced SJS and TEN.

DATA SOURCES A comprehensive search of the following data sources was performed without language restriction from the inception of the database until January 8, 2013: EMBASE, PubMed, clinicaltrials.gov, Cochrane Library, IPA (International Pharmaceutical Abstracts), HuGENet (Human Genome Epidemiology Network), and CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the reference lists of identified studies.

STUDY SELECTION Inclusion criteria were studies that investigated the relationship between *HLA-B*1502* and carbamazepine-induced SJS and TEN and that reported sufficient data for calculating the frequency of *HLA-B*1502* carriers among cases and controls. The search yielded 525 articles, of which 16 met the inclusion criteria. The studies included 227 SJS or TEN cases, 602 matched control subjects, and 2949 population control subjects.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted the following data: study design, eligibility criteria, diagnostic criteria, patient demographics, genotype distribution, *HLA-B* genotyping technique, selection of cases and controls, dosage of carbamazepine and duration of use, and results of Hardy-Weinberg equilibrium in the control group. The Newcastle-Ottawa Scale was used to assess the quality of studies. The overall odds ratios (ORs) with corresponding 95% CIs were calculated using a random-effects model. The primary analysis was based on matched control studies. Subgroup analyses by race/ethnicity were also performed.

MAIN OUTCOME AND MEASURE The primary outcome was carbamazepine-induced SJS and TEN. The outcome measure is given as an overall OR.

RESULTS The summary OR for the relationship between *HLA-B*1502* and carbamazepine-induced SJS and TEN was 79.84 (95% CI, 28.45-224.06). Racial/ethnic subgroup analyses yielded similar findings for Han-Chinese (115.32; 18.17-732.13), Thais (54.43; 16.28-181.96), and Malaysians (221.00; 3.85-12 694.65). Among individuals of white or Japanese race/ethnicity, no patients with SJS or TEN were carriers of the *HLA-B*1502* allele.

CONCLUSIONS AND RELEVANCE We found a strong relationship between the *HLA-B*1502* allele and carbamazepine-induced SJS and TEN in Han-Chinese, Thai, and Malaysian populations. *HLA-B*1502* screening in patients requiring carbamazepine therapy is warranted.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Nathorn Chaiyakunapruk, PharmD, PhD, Discipline of Pharmacy, Monash University Sunway Campus, Jalan Lagoon Selatan, 46150 Bandar Sunway, Selangor, Malaysia (nathorn.chaiyakunapruk@monash.edu).

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening conditions affecting the skin and mucous membranes.[1] Both SJS and TEN are characterized by blisters arising on purple macules. Lesions are widespread and usually predominate on the trunk of the body. The percentage of skin detachment body surface area differentiates SJS and TEN.[2] Although the incidence of SJS and TEN is low (0.4-6 cases per million persons per year),[1,3] mortality rates are as high as 5% to 12.5% for SJS, 33.3% for SJS and TEN overlap, and 30% for TEN.[1,4]

The primary identifiable causative agent of SJS and TEN is medication use (almost 80% of cases).[1] Other factors implicated include chemicals, viral infection, immunizations, and mycoplasma pneumonia. Several classes of medication have been strongly associated with SJS and TEN, including antibiotics, antiepileptic drugs, and xanthine oxidase inhibitors.[1] Carbamazepine is the most common cause of SJS or TEN.[5,6] A European study[7] found that the risks of SJS or TEN among carbamazepine and phenytoin users were more than 90 and 53 times greater than those of nonusers, respectively.

Multiple investigators have reported a relationship between *HLA* genes and SJS and TEN induced by carbamazepine. Specifically, the *HLA-B*1502* allele (OMIM 142830.0002) has been associated with carbamazepine-induced SJS and TEN.[8-11] In addition to carbamazepine, allopurinol can be a causative agent of SJS and TEN, particularly among those carrying the *HLA-B*5801* allele.[12] Based on these observational studies, the US Food and Drug Administration published an alert to health care professionals that severe allergic skin reactions can be caused by carbamazepine use in patients with the *HLA-B*1502* allele and recommended screening for the allele before initiation of carbamazepine therapy in patients of Asian ancestry.[13]

Despite the alert from the US Food and Drug Administration, some studies[9,11,14-16] have demonstrated no such association in the Japanese population. This difference likely reflects race/ethnicity variation, as well as nonreporting of less severe cutaneous drug reactions.[9,11,14-16] To fully understand the relationship between *HLA-B*1502* and SJS and TEN among carbamazepine users, a systematic review identifying all studies assessing such association is needed. A transparent and reproducible process may be provided using a systematic review approach. This method can elucidate potential similarities and differences that may explain the findings. Therefore, this study was undertaken to systematically review all relevant studies and to quantitatively synthesize the magnitude of the relationship between the *HLA-B*1502* allele and carbamazepine-induced SJS and TEN.

Methods

Data Sources and Search Strategy

We searched EMBASE, PubMed, clinicaltrials.gov, The Cochrane Library, IPA (International Pharmaceutical Abstracts), HuGENet (Human Genome Epidemiology Network), and CINAHL (Cumulative Index to Nursing and Allied Health Literature). All databases were searched from their inception until January 8, 2013. Searches were performed using keywords and synonyms for *HLA-B* and carbamazepine and relevant terms for SJS and TEN. For PubMed and The Cochrane Library, Medical Subject Headings were searched for *HLA-B* and carbamazepine and for SJS and TEN. There was no language or study design restriction, but only human studies were included. Additional studies were retrieved from the reference lists of the selected articles.

Study Selection

Two reviewers (W. Tangamornsuksan and R.S.) independently assessed abstracts and titles retrieved from the comprehensive searches for study inclusion. The inclusion criteria were studies that (1) investigated the relationship between *HLA-B*1502* and carbamazepine-induced SJS and TEN and (2) reported sufficient data for calculating the frequency of *HLA-B*1502* carriers among cases and controls. Any disagreements were discussed until consensus between the 2 reviewers could be reached.

Data Extraction and Quality Assessment

All articles were extracted independently by the reviewers; discrepancies were resolved by discussion. The following data were extracted from each study: study design, eligibility criteria, diagnostic criteria, patient demographics, genotype distribution, *HLA-B* genotyping technique, selection of cases and controls, dosage of carbamazepine and duration of use, and results of Hardy-Weinberg equilibrium (a state of equilibrium under the mendelian law of genetic inheritance) in the control group. Hardy-Weinberg equilibrium was tested to check if the included individuals were in equilibrium for the frequencies of genotypes.[17,18] Equilibrium implies that the included individuals are likely representative of the population.[19,20] We used the Newcastle-Ottawa Scale[21] to assess the quality of the studies included in the review. This scale is an 8-item instrument, categorized into the following 3 domains: selection of participants, comparability between 2 groups, and the assessment of exposures and outcomes. A system of stars is used to provide quality ratings for studies.

Data Analysis

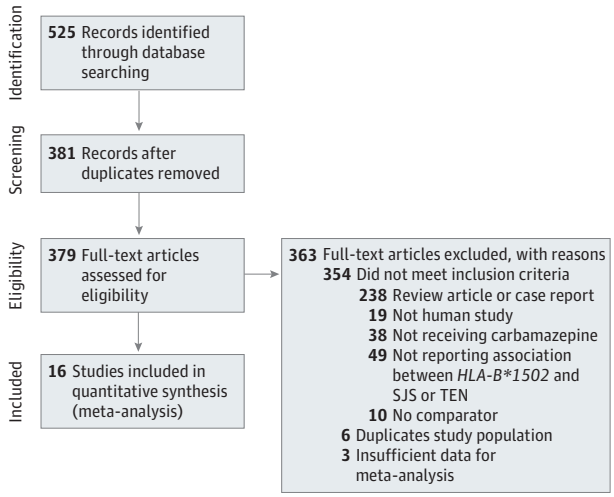
The overall odds ratios (ORs) with corresponding 95% CIs were calculated to determine the relationship between the presence of *HLA-B*1502* in at least 1 allele and carbamazepine-induced SJS and TEN. All analyses were performed with the method by DerSimonian and Laird[22] using a random-effects model. The analyses were also performed separately on studies using different types of control groups (eg, control subjects obtained from the study [matched control study] or control subjects obtained from the population database [population study]). The primary outcome measure was analyzed using the matched control study. Subgroup analyses by race/ethnicity were also performed to determine the robustness of the findings. Statistical heterogeneity was assessed via the Q statistic and I^2 tests.[23] $P \leq .10$ indicated heterogeneity between studies. I^2 values of 25% and 50% denoted low heterogeneity and moderate heterogeneity, respectively, across studies.[24] Funnel plot, Begg test, and Egger test were used to evaluate publication bias.[25,26]

Results

Study Selection

In total, 525 articles were identified by the search. Sixteen articles[14,16,27-40] met the inclusion criteria. Some SJS and TEN cases included in the studies by Chung et al,[9] Ikeda et al,[15] Wang et al,[41] and Kulkantrakorn et al[42] were also in the studies by Hung et al,[28] Kaniwa et al,[29] Shi et al,[36] and Tassaneeyakul et al,[37] respectively. In addition, 1 study[43] and 2 abstracts[44,45] potentially met the inclusion criteria but lacked key information. Of the original 525 articles, 16 remaining studies were included in the meta-analysis (**Figure 1**). No additional articles were identified via a review of the bibliographies of the included studies.

Figure 1. Flow Diagram for Study Identification, Inclusion, and Exclusion



SJS indicates Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Study Characteristics

Characteristics of the included studies are summarized in **Table 1**. The studies included 227 SJS or TEN cases[14,16,27-40]; in addition, there were 602 matched control subjects[14,28,30-32,35-40] and 2949 population control subjects.[16,27,29,30,33,34] Eleven studies[14,28,30-32,35-40] were conducted using matched controls, while 6 studies[16,27,29,30,33,34] used the population as controls. Fifteen studies were conducted among Asian populations, including 1 study[30] in Koreans, 1 study[34] in Indians, 2 studies[32,37] in Thais, 2 studies[27,38] in Malaysians, 3 studies[16,29,35] in Japanese, and 6 studies[28,31,36,39-41] in Han-Chinese. Two studies[14,34] examined individuals of white race/ethnicity, while 3 studies[27,31,33] evaluated multiethnic populations (Table 1).

Among studies having matched controls, the mean ages of included patients were 54 years[28,30,32,35-40] and 47 years[28,30,36-40] in cases and controls, respectively; 42.6% (75 of 176) of cases[28,30,32,35-40] and 47.0% (206 of 438) of controls[28,30,36-38,40] were male. Among studies[29,30,33,34] using the population as controls, the mean age of included patients was 51 years in cases; 40.4% (21 of 52) of cases were male,[29,30,33,34] while age and sex data were not reported for controls.

Four studies[28,30,36,39] and 2 studies[30,36] reported the mean carbamazepine dosages in the case and control groups, which

Table 1. Characteristics of Studies Included in the Meta-analysis

Source	Race/Ethnicity	Nationality	Control	No. Positive for *HLA-B*1502*/Total No.		Matching Criteria	Newcastle-Ottawa Scale Score
				Case	Control		
Alfirevic et al,[14] 2006	White	European	Matched	0/2[a]	0/43	Drug, hospital	4
Chang et al,[27] 2011	Multiethnic	Mixed population[b]	Population	12/16	47/300	NR	4
Hung et al,[28] 2006	Asian	Han-Chinese	Matched	59/60	6/144	Drug, hospital	6
Kaniwa et al,[29] 2008	Asian	Japanese	Population	0/7[c]	0/493	NR	4
Kashiwagi et al,[16] 2008	Asian	Japanese	Population	0/2[a]	1/371	NR	4
Kim et al,[30] 2011	Asian	Korean	Population and matched	1/7	2/485 For population study, 0/50 for matched study	NR for population study, drug and hospital for matched study	6 5
Liao et al,[31] 2009	Asian	Han-Chinese	Matched	6/6	16/76	Drug, hospital	5
Locharernkul et al,[32] 2008	Asian	Thai	Matched	6/6[a,c]	8/42	Drug, hospital	6
Lonjou et al,[33] 2008	Asian, white	Mixed population[d]	Population	4/12[c]	1/1290	NR	4
Mehta et al,[34] 2009	Indian	Indian	Population	6/8	0/10	NR	4
Niihara et al,[35] 2012	Asian	Japanese	Matched	0/3	0/33	Drug, hospital	6
Shi et al,[36] 2012	Asian	Han-Chinese	Matched	13/18	12/93	Drug, hospital	6
Tassaneeyakul et al,[37] 2010	Asian	Thai	Matched	37/42	5/42	Drug, hospital	5
Then et al,[38] 2011	Asian	Mixed population[e]	Matched	6/6	0/8	Drug, hospital	4
Wu et al,[39] 2010	Asian	Han-Chinese	Matched	8/8	4/50	Drug, hospital	5
Zhang et al,[40] 2011	Asian	Han-Chinese	Matched	16/17	2/21	Drug, hospital	5

Abbreviation: NR, not reported.

[a] Only patients who developed Stevens-Johnson syndrome or toxic epidermal necrolysis were included.

[b] Chinese, Indian, and Malaysian.

[c] Only patients who received carbamazepine were included. All 4 cases with positive *HLA-B*1502* were of Asian ancestry.

[d] European and Asian (Pakistan, Reunion, Vietnam, China, Cambodia, and India) and African (Senegal).

[e] Chinese and Malaysian.

Table 2. Reported Odds Ratios for the Included Studies and Summary Odds Ratios Categorized by Type of Study and by Race/Ethnicity

Source	No. Positive for *HLA-B*1502*/Total No.		Odds Ratio (95% CI)
	Case	Control	
Matched Control			
White race/ethnicity			
Alfirevic et al,[14] 2006	0/2	0/43	NA
Asian			
Han-Chinese			
Hung et al,[28] 2006	59/60	6/144	1357.00 (159.84-11 520.40)
Liao et al,[31] 2009	6/6	16/76	47.67 (2.55-890.45)
Shi et al,[36] 2012	13/18	12/93	17.55 (5.31-58.06)
Wu et al,[39] 2010	8/8	4/50	114.83 (6.25-2110.92)
Zhang et al,[40] 2011	16/17	2/21	152.00 (12.59-1834.92)
Subtotal (I^2 = 71.3%, P = .008)	NA	NA	115.32 (18.17-732.13)
Thai			
Locharernkul et al,[32] 2008	6/6	8/42	52.76 (2.70-1031.31)
Tassaneeyakul et al,[37] 2010	37/42	5/42	54.76 (14.62-205.13)
Subtotal (I^2 = 0.0%, P = .98)	NA	NA	54.43 (16.28-181.96)
Korean			
Kim et al,[30] 2011	1/7	0/50	23.31 (0.86-633.94)
Malaysian			
Then et al,[38] 2011	6/6	0/8	221.00 (3.85-12 694.65)
Japanese			
Niihara et al,[35] 2012	0/3	0/33	NA
Overall (I^2 = 39.0%, P = .98)	NA	NA	79.84 (28.45-224.06)
Population Control			
White race/ethnicity			
Lonjou et al,[33] 2008	4/12	1/1290	644.50 (64.69-6431.36)
Indian			
Mehta et al,[34] 2009	6/8	0/10	54.60 (2.25-1326.20)
Asian			
Chang et al,[27] 2011	12/16	47/300	16.15 (4.99-52.22)
Kaniwa et al,[29] 2008	0/7	0/493	NA
Kashiwagi et al,[16] 2008	0/2	1/371	49.40 (1.59-1531.08)[a]
Kim et al,[30] 2011	1/7	2/485	40.25 (3.20-265.09)
Subtotal (I^2 = 0.0%, P = .68)	NA	NA	20.64 (7.47-57.07)
Overall (I^2 = 53.1%, P = .07)	NA	NA	57.56 (12.50-265.09)

Abbreviation: NA, not applicable.

[a] Odds ratio was estimated based on the continuity correction for zero events.[46]

were 559 mg/d and 514 mg/d, respectively. One population control study[30] reported this information, which was 243 mg/d for the case group.

Most studies (8 of 11 [72.7%]) using matched controls specified the use of criteria by Roujeau and Stern[1] and by Roujeau et al[7] as SJS and TEN diagnostic criteria for cases, while 4 studies[14,16,31,38] provided no information on the criteria used. Among studies using population controls, 3 studies[27,33,38] reported use of the criteria by Roujeau and colleagues.[1,7] In all studies with matched controls, patients without SJS and TEN who had used carbamazepine for at least 3 to 6 months were included in the control group, while patients who developed SJS and TEN within 2 to 12 weeks after the start of carbamazepine therapy were included in the case group.

Only 2 studies[28,33] reported Hardy-Weinberg equilibrium, and these confirmed no departure from equilibrium. Characteristics of the alleles (heterozygous vs homozygous) in cases and controls were reported in 2 studies.[32,34] All 6 patients in the study by Mehta et al[34] had a heterozygous *HLA-B*1502* allele, while 20 of 21 patients in the study by Locharernkul et al[32] had a heterozygous allele. Eleven studies[16,27,30-34,36-38,40] identified *HLA-B*1502* using polymerase chain reaction sequence-specific primers, 3 studies[28,29,39] used polymerase chain reaction sequence-based typing, and 2 studies[14,32] used polymerase chain reaction sequence-specific oligonucleotides. None of the included studies described a blinding procedure for personnel performing the genotyping.

Quality Assessment

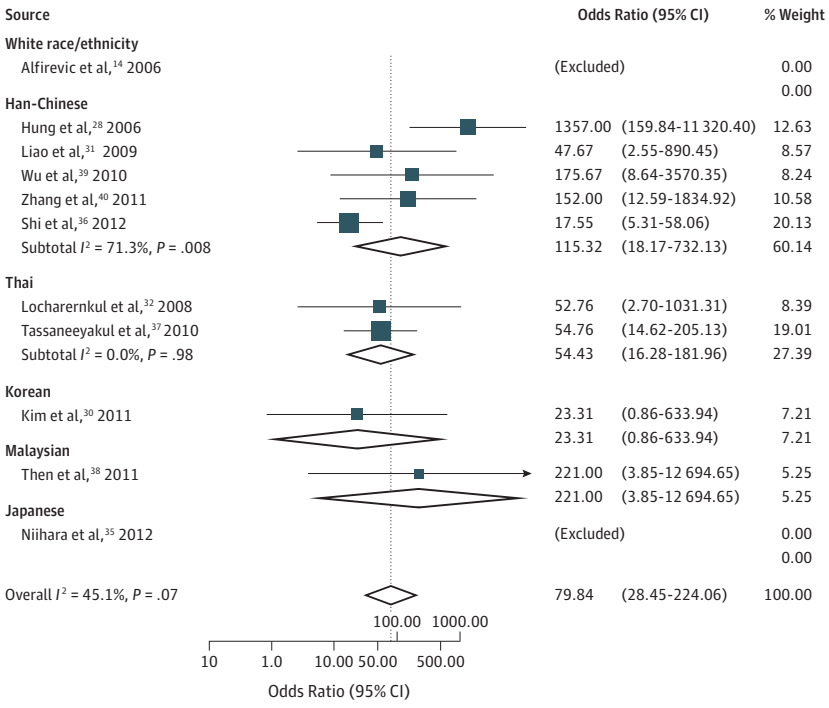
The methodological quality of all studies was summarized as a mean Newcastle-Ottawa Scale score of 5 (range, 4-6; maximum score, 9). These results are given in Table 1.

Quantitative Synthesis

Analysis Using Matched Control Studies

Eleven studies[16,27,30-34,36-38,40] were included in a comparison of the *HLA-B*1502* carrier frequencies in the cases and carbamazepine-tolerant controls. There were 175 SJS or TEN cases

Figure 2. Random-Effects Meta-analyses of Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Among Carriers of the *HLA-B*1502* Allele



Forest plot of subgroup analyses according to race/ethnicity. Width of the box indicates the precision of the estimates; diamond, the overall summary estimate for the analysis (width of the diamond represents the 95% CI).

and 602 matched controls. Of the controls, 53 were carriers of the allele, while a much larger proportion of the cases (152 of 175) carried the allele. We found a clear relationship between *HLA-B*1502* and carbamazepine-induced SJS and TEN (summary OR, 79.84; 95% CI, 28.45-224.06). Heterogeneity was minimal (I^2 = 45.1%) and was not significant by the *Q* statistic (*P* = .07). There was no apparent publication bias by Begg test (*P* = .92), Egger test (*P* = .23), or funnel plot.

Analysis Using Population Control Studies

Six studies[16,27,29,30,33,34] with 52 SJS or TEN cases and 2949 population controls were included in a separate analysis of carrier frequency to test the relationship between the *HLA-B*1502* genotype and carbamazepine-induced SJS and TEN compared with the general population. Cumulative carrier frequencies for these 6 studies were 23 of 52 for cases and 51 of 2949 for population controls. The relationship between the *HLA-B*1502* genotype and carbamazepine-induced SJS and TEN compared with the general population was statistically significant (summary OR, 57.56; 95% CI, 12.50-265.09). Heterogeneity was present (I^2 = 53.1%, *P* = .007). There was no apparent publication bias by Begg test (*P* = .31) or Egger test (*P* = .81) and with a funnel plot.

Subgroup Analyses

Subgroup analysis in the selected matched control studies[14,28,30-32,35-40] according to race/ethnicity yielded similar and significant findings. Carbamazepine-induced SJS or TEN was associated with the *HLA-B*1502* allele in Han-Chinese,[28,31,36,39,40] Thai,[32,37] Korean,[30] and Malaysian[38] patients. The summary ORs for Han-Chinese, Thai, Korean, and Malaysian populations are given in **Table 2** and in **Figure 2**. The summary OR for Han-Chinese was 115.32 (95% CI, 18.17-732.13), with I^2 heterogeneity of 71.3%. Such heterogeneity probably arose from a nonhomogeneous patient population from the north and south of China.[47] This was confirmed by a reanalysis that excluded this study and yielded similar results (OR, 113.65; 95% CI, 44.20-292.22) but with much less heterogeneity (I^2 = 14.4%). In the sole matched control study among individuals of white[14] and Japanese[35] race/ethnicity, no patients carried the *HLA-B*1502* allele.

Discussion

Our results indicate that the *HLA-B*1502* allele is strongly associated with increased risk of developing SJS and TEN in patients using carbamazepine, especially Asians. This severe adverse event could be prevented if genetic information were known a priori. Physicians and policymakers should consider our findings to support the implementation of genetic testing before initiation of carbamazepine therapy.

Data reveal a high risk of developing SJS and TEN among carbamazepine users with *HLA-B*1502*. For Han-Chinese, Thais, Koreans, and Malaysians, the risks of SJS and TEN among carbamazepine users carrying the *HLA-B*1502* allele are approximately 115-fold, 60-fold, 25-fold, and 220-fold increases, respectively.

These observed racial/ethnic differences could be explained by the fact that *HLA-B*1502* may not be the only gene associated with SJS and TEN in patients using carbamazepine. For example, another *HLA* allele (*HLA-A*3101*) is related to SJS and TEN; the ORs for carriers of this gene using carbamazepine are approximately 26-fold higher for Europeans[48] and 11-fold higher for Japanese.[49] Furthermore, Hung et al[28] reported that *HLA-A*3101* was associated with carbamazepine-induced maculopapular eruptions (OR, 17.5; 95% CI, 4.6-66.5) and hypersensitivity syndrome (OR, 7.1; 95% CI, 3.1-16.5) in a Han-Chinese population. Similar to the observed relationship between *HLA-B*1502* and SJS and TEN among carbamazepine users, there are some examples of associations in which more than 1 gene has a major role.[50,51]

Although the mechanism by which *HLA-B*1502* contributes to SJS and TEN among carbamazepine users is not fully understood, it is well recognized that HLA-B molecules supply endogenous or processed exogenous antigens to T cells, eliciting an adaptive immune response. It seems that a specific *HLA* allele is required for the activation of drug-specific T cells by the culprit drug. The T-cell receptor of the effector T cell is thought to recognize the drug-peptide complex bound by the specific HLA-B molecule on the antigen-presenting cell, resulting in the release of immune mediators and leading to robust adaptive immune reactions in severe cutaneous reactions.[52-54]

Our systematic meta-analysis has several limitations. First, this study focused only on the relationship between the *HLA-B*1502* allele and carbamazepine-induced SJS and TEN. Other genes that may be associated with SJS and TEN (such as *HLA-A*3101*) were excluded from our study. Second, an article[43] and 2 abstracts[44,45] that potentially met our study criteria were not included in the meta-analysis because they did not provide the number of control patients, which was important information for the analysis. Third, only 2 studies[28,33] among 16 articles provided Hardy-Weinberg equilibrium information, preventing us from assessing the representativeness of the controls.

Our study reveals that *HLA-B*1502* is strongly associated with the development of SJS and TEN. The prevalence of *HLA-B*1502* among residents of southeast Asian countries was reported to be 8%.[9,55] This is against the background of a high incidence of SJS and TEN among this population (8 cases per 1 million person-years).[56,57] In Thailand, Singapore, and Malaysia, carbamazepine use represents up to one-third of all SJS and TEN cases.[56-58] The relationship between the *HLA-B*1502* allele and carbamazepine-induced SJS and TEN was strong in Thai (OR, 54.43) and Malaysian (OR, 221.00) populations in our study, reflecting the high disease risk associated with *HLA-B*1502* carrier status among patients of Asian ancestry. Because carbamazepine use for epilepsy is normally a long-term therapy, the safety requirements are high. It is important to consider genetic screening among populations at high risk, such as those from southeast Asian countries. However, there is a strong need to consider other factors such as feasibility, ethical and legal issues, and cost-effectiveness before implementation of such genetic screening.

In conclusion, we found a strong relationship between *HLA-B*1502* and carbamazepine-induced SJS and TEN in Han-Chinese, Thai, and Malaysian populations. Recognition of *HLA-B* allele status before initiation of the drug may be beneficial to some groups of patients. Such information will assist physicians in determining the optimal drug therapy.

ARTICLE INFORMATION

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Author Affiliations: Center of Pharmaceutical Outcomes Research, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand (Tangamornsuksan, Chaiyakunapruk); Discipline of Pharmacy, Monash University Sunway Campus, Selangor, Malaysia (Chaiyakunapruk); School of Population Health, University of Queensland, Brisbane, Australia (Chaiyakunapruk); School of Pharmacy, University of Wisconsin–Madison (Chaiyakunapruk); Kasemradsriburin Hospital, Chiang Rai, Thailand (Somkrua); Center of Excellence for Environmental Health and Toxicology, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand (Lohitnavy); Pharmacokinetic Research Unit, Faculty of Pharmaceutical Sciences, Phitsanulok, Thailand (Lohitnavy); Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (Tassaneeyakul); Research and Diagnostic Center for Emerging Infectious Diseases, Khon Kaen University, Khon Kaen, Thailand (Tassaneeyakul).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tangamornsuksan, Chaiyakunapruk, Somkrua, Lohitnavy.
Acquisition of data: Tangamornsuksan, Tassaneeyakul.
Analysis and interpretation of data: Tangamornsuksan, Chaiyakunapruk, Tassaneeyakul.
Drafting the manuscript: Tangamornsuksan, Chaiyakunapruk, Lohitnavy.
Critical revision of the manuscript for important intellectual content: All authors.

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NOTABLE NOTES

Presidential Practice of Dermatology

Loren Zech, MD, PhD; Bryce Turner, BA; Scott A. Norton, MD, MPH

Lyndon Johnson, the 36th President of the United States, had many careers en route to the White House (schoolteacher, local administrator, naval officer, and elected public official), but his brief stint as an amateur dermatologist is generally overlooked. Johnson's unorthodox approach to treating severe facial acne was first tried while he was an undergraduate at Southwest Texas State Teachers' College. A classmate who witnessed the episode is quoted verbatim in the first volume of Robert Caro's monumental biography of Johnson[1]:

One student, a Bohemian farm boy, was generally immune from practical jokes because he was so "slow" and gullible—some students believed he might be slightly retarded—as to be too defenseless a target. This student had a severe case of acne, and one evening, talking with Johnson, ... he said girls wouldn't go out with him because of it.

Lyndon said to him that the cure was to get fresh cow manure and put it on your face. He said, "Oh, go on," and Lyndon said, "Didn't you ever turn over a cow pile and see how white the grass was underneath, how the manure bleached the grass?"... Lyndon tells him to take a towel and cut eyeholes in it and wrap it around his face. He...came into our room and asked how it was, and Lyndon said, "You don't have enough on to do any good." He made him put more on. In the morning, he smelled so bad, you couldn't go near him.

On the one hand, we do not have long-term follow-up of Johnson's initial patient, and, as with many *n*-of-1 clinical trials, we lack adequate data on safety and efficacy on which to base further recommendations. Interest in alternative interventions for severe acne waned greatly with the success of systemic retinoids. Furthermore, use of topical bovine excrement would certainly test the limits of acceptability for today's discerning patients, even with a marketing strategy that touts its natural origins.

On the other hand, medicinal formulations of equine urine, porcine digestive hormones, bovine bile, and other below-the-diaphragm excretions are regularly used in medicine and generally accepted by the wider public. Human feces, in the form of an allogeneic transplant, is now an accepted treatment for *Clostridium difficile* enteritis.[2] Evidence of the microbiome's role in healthy and diseased skin, and its potential manipulation in therapy, is piling up. Kang et al[3] have shown that some human fecal enterococci have in vitro activity against *Proprionobacterium acnes*, which suggests further exploration of fecotherapy in dermatology.

Author Affiliations: Georgetown University/Washington Hospital Center, Department of Dermatology, Washington, DC (Zech, Norton); Georgetown University School of Medicine, Washington, DC (Turner).

Corresponding Author: Loren Zech, MD, PhD, Department of Dermatology, Georgetown University Hospital, Washington Hospital Center, 110 Irving St NW, Room 2B-44, Washington, DC 20010 (loren.zech@medstar.net; loren.zech@gmail.com).

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