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FULL-LENGTH ORIGINAL RESEARCH

HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese

*Ying-Kit Cheung, †Suk-Hang Cheng, *Ernest J. M. Chan, ‡Su V. Lo, †Margaret H. L. Ng, and *§Patrick Kwan

*Departments of Medicine and Therapeutics; †Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; ‡Division of Planning & Strategy, Hospital Authority Head Office, Hong Kong, China; and §Departments of Medicine and Neurology, The University of Melbourne, Royal Melbourne Hospital, Melbourne, Australia

Summary

Purpose: HLA-B*15:02 screening is recommended before starting carbamazepine in Han Chinese and Southeast Asians because the allele is strongly predictive of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) induced by the drug. We examined whether other HLA-B alleles are also involved and whether the association extends to other antiepileptic drugs (AEDs).

Methods: Cases of SJS/TEN induced by any AEDs were recruited and matched (1:5) with AED-tolerant controls. Carrier rates of HLA-B alleles, determined by direct sequencing, were compared between cases and controls. Results were meta-analyzed with previous studies to examine the associations between HLA-B*15:02 and SJS/TEN induced by phenytoin and lamotrigine.

Key Findings: A total of 55 cases (27 carbamazepine, 15 phenytoin, 6 lamotrigine, 7 other AEDs) and 275 controls were recruited. In drug-specific analysis, the carrier rate of HLA-B*15:02 was significantly higher in carbamazepine-SJS/TEN cases compared with carbamazepine-tolerant controls (92.3% vs. 11.9%; $p = 3.51 \times 10^{-18}$; odds ratio (OR) 89.25; 95% confidence interval (CI) 19.25–413.83), and also in phenytoin-SJS/TEN cases compared with phenytoin-tolerant controls (46.7% vs. 20.0%; p = 0.045; OR 3.50; 95% CI 1.10–11.18). Meta-analyses showed a strong association of HLA-B*15:02 with phenytoin-SJS/TEN ($p < 3 \times 10^{-4}$; OR 4.26; 95% CI 1.93–9.39) and, to a lesser extent, lamotrigine-SJS/TEN (p = 0.03; OR 3.59; 95% CI 1.15–11.22). Compared with drug-tolerant controls, the carrier rates of HLA-B*40:01 and HLA-B*58:01 were lower in cases of SJS/TEN induced by carbamazepine (p = 0.004) and other AEDs (p = 0.009), respectively.

Significance: SJS/TEN induced by carbamazepine and phenytoin is strongly and moderately associated with HLA-B*15:02 in Han Chinese, respectively. Possible protective associations with HLA-B*40:01 and HLA-B*58:01 warrant further investigation.

KEY WORDS: Antiepileptic drugs, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Pharmacogenetics, Human leukocyte antigen.

Antiepileptic drugs (AEDs) are one of the most common groups of medications to induce rare but severe cutaneous adverse drug reactions (cADRs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome (HSS; Svensson et al., 2001). SJS and TEN belong to the same disease spectrum characterized by rapidly developing blistering exanthema of macules and target-like lesions accompanied by, to different extents, cutaneous and mucosal detachment (Roujeau & Stern, 1994). Up to 30% of patients with severe cADRs die, mostly from sepsis and respiratory distress (Svensson et al., 2001). These reactions are generally considered idiosyncratic and unpredictable irrespective of dosage (Yang et al., 2011).

Our previous study in Hong Kong Han Chinese found that the presence of HLA-B*15:02 greatly increased the risk of SJS or TEN, but not milder maculopapular exanthema (MPE) or HSS, induced by carbamazepine (CBZ; Man et al., 2007). The findings confirmed previous reports in Taiwan Chinese (Chung et al., 2004; Hung et al., 2006). These early studies reported an almost 100% carrier rate in patients with CBZ-SJS/TEN compared with 3–15% in the CBZ-tolerant controls. Similar association was subsequently reported in Han Chinese living in different parts of mainland China (Wu et al., 2010; Wang et al., 2011; Zhang et al., 2011), as well as other south/southeast Asian populations including Thai (Locharernkul et al., 2008; Tassaneeyakul et al., 2010), Malay (Chang et al., 2011), and Indian (Mehta et al., 2009). However, some of the cases of CBZ-SJS/TEN in these later studies did not carry the HLA-B*15:02 allele (Zhang et al., 2011; Shi et al.,

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Address correspondence to Patrick Kwan, Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong, China. E-mail: patrickkwan@cuhk.edu.hk

2012), suggesting that other genetic variants may play a role. Screening for HLA-B*1502 has been recommended by the U.S. Food and Drug Administration (FDA) prior to starting CBZ in patients with ancestry from these populations since December 2007 (U.S. Food & Drug Administration, 2012). However, although physicians need to consider alternative AEDs in patients who carry HLA-B*15:02 to avoid severe cADRs, it remains unclear whether the association extends to other high-risk, structurally similar compounds such as phenytoin (PHT) and lamotrigine (LTG; Locharernkul et al., 2008; Shankarkumar et al., 2009; An et al., 2010; Hung et al., 2010; Shi et al., 2011). Apart from HLA-B*15:02, other alleles of the HLA-B locus are known to be predictive of drug-induced hypersensitivity reactions, including HLA-B*57:01 for abacavir-hypersensitivity reaction (Mallal et al., 2008) and HLA-B*58:01 for allopurinol-SJS/TEN (Hung et al., 2005), further implying the important role of HLA-B in the pathogenesis of severe cADRs.

We conducted a Hong Kong–wide study to examine the association of HLA-B alleles with SJS/TEN induced by different AEDs in Han Chinese. To clarify the possible associations of HLA-B*15:02 with PHT- and LTG-SJS/TEN, we also combined our results in meta-analyses with previous studies.

Materials and Methods

Cases

This case–control study was approved by ethics committees of the participating hospitals, and all subjects provided written informed consent. Patients who developed SJS/TEN induced by any available AEDs from January 1, 1993 to June 30, 2009 were identified by interrogating the electronic data warehouse of the Hospital Authority (HA), which provides public health care to >90% of the 7 million population in Hong Kong. Its electronic data warehouse and patient record (ePR) system, introduced since 1993, contains diagnosis and diagnostic codes (ICD-9 CM), outpatient and inpatient notes, information on medications dispensed, history of drug allergies, and investigation results of all patients attending public hospitals. SJS/TEN was defined according to established criteria and in line with previous studies (Roujeau & Stern, 1994; Hung et al., 2006; Man et al., 2007). Ethnic Han Chinese patients who developed SJS/TEN within 12 weeks after commencing an AED (for any indication) and for which no other causes were found were eligible for inclusion as cases. Patients who were younger than the age of 13 years, unable to provide informed consent or a blood/saliva sample, were excluded.

Eligible patients (or their parents/legal guardians for minors) were contacted and invited for screening. During the study visit, clinical information (particularly concerning the episode of SJS/TEN) was verified against the ePR and a venous blood sample was obtained. For those consented to the study but unable or unwilling to attend the hospital, their clinical information was verified over the telephone and they were sent by mail a saliva collection kit for the collection of salivary samples. The collected saliva samples were sent back for DNA extraction.

Controls

Cases were matched with controls in age and AED prescribed in the ratio of 1:5. Controls were patients who had taken the AEDs for at least 3 months without developing cADRs. They were identified from a DNA bank of Han Chinese epilepsy patients established by the research team in Hong Kong, as described previously (Kwan et al., 2008). Detailed phenotype data (including history of AED use) were collected from every patient.

HLA-B genotyping

DNA collected from blood samples was extracted using QIAamp DNA kit (Qiagen, Hilden, Germany). DNA collected from saliva was extracted using Oragene DNA Self-Collection Kit (DNA Genotek, Kanata, ON, Canada). Polymerase chain reaction (PCR) was performed with primers spanning exon 2–3 of HLA-B region (forward: 5′-GG GAGGAGCGAGGGGACCSCAG-3′; reverse: 5′-GGAGG CCATCCCCGGCGACCTAT-3′), with reaction conditions according to the IHWG Technical Manual (Tilanus et al., 2002). The amplicon was excised and purified by Gel Advanced DNA extraction system (Viogene, New Taipei City, Taiwan). DNA sequencing for HLA-B region was performed using ABI 3730xl DNA sequencer (Applied Biosystems, Grand Island, NY, U.S.A.) with primers on exons 2 (forward: 5′-GGGCGCAGGACCYGRGGA-3′; reverse: 5′-GGTCACTCACCGKCCTCG-3′) and 3 (forward: 5′-GGG GCCAGGGTCTCACA-3′; reverse: 5′-CCCACTGCCCCT GGTACC-3′). The resulting sequences were analyzed using SBTengine (Genome Diagnostics, Utrecht, The Netherlands).

Meta-analyses

Previous case–control studies on the association between HLA-B*15:02 and PHT- or LTG-SJS/TEN were identified from the following databases: MEDLINE, MEDLINE In-Process, Excerpta Medica Database (EMBASE), and Cochrane library. Studies were limited to the search terms "human leukocyte antigen" or "HLA" AND "Stevens-Johnson syndrome" or "toxic epidermal necrolysis." The search results were further limited to "phenytoin" for identifying studies related to PHT and to "lamotrigine" for searching LTG-related studies. All key words were searched from inception of each database to July 5, 2012, without language restriction. Publications were restricted to human studies. References of included publications were reviewed for additional suitable articles. The studied ethnicity was limited to Han Chinese. Review articles, commentary, expert opinion, editorial articles, case reports, conference abstracts, and repeated studies

were excluded. Identified articles were examined by two independent reviewers (Y.K.C. and P.K.) for inclusion in the meta-analyses. Disagreements were resolved by consensus through discussion.

Statistical analysis

Because HLA-B*15:02 was the most common HLA-B allele among the cases, the primary analysis was the association between HLA-B*15:02 and SJS/TEN induced by various AEDs. Two-tailed Pearson chi-square test or Fisher's exact test used to compare the carrier rates of HLA-B*15:02 in patients with AED-SJS/TEN (cases) with the AED-tolerant patients (controls) was performed by IBM SPSS Statistics version 19.0 software (Armonk, NY, U.S.A.). We also examined whether the presence of other common HLA-B alleles (arbitrarily defined as being present in at least 3% of controls) was associated with an increased or decreased risk of AED-SJS/TEN in all subjects collectively. Alleles with $p < 0.05$ were further tested in CBZ cases and non-CBZ cases with their matching controls separately. The strength of association was estimated by calculating the OR with 95% CI from the corresponding 2×2 contingency table. Bonferroni correction was applied to adjust for multiple comparisons. In the meta-analyses, pooled OR and 95% CI from different studies were calculated in a fixed-effect model ($I^2 < 25\%$) using Mantel-Haenszel statistics. Heterogeneity was tested by Cochran chi-square and I-square (I^2) tests. Cochran chi-square test with $p > 0.10$ indicated statistically insignificant heterogeneity. The overall effects were calculated by combined *z*-values, with $p < 0.05$ indicating statistical significance. Meta-analyses were performed using Review Manager version 5 software (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

Results

Characteristics of patients

A total of 55 cases (54.5% female) were recruited. Their mean age at onset of SJS/TEN was 38 years (range 6–77; standard deviation [SD] 17). SJS/TEN was induced by CBZ in 27 patients and by other AEDs in 28 including 15 PHT, 6 LTG, 3 sodium valproate (VPA), 2 phenobarbital (PB), one gabapentin (GBP), and one levetiracetam (LEV). Four of the CBZ, one LTG, and one PB cases had been included in our previous report that recruited patients from only one of the participating hospitals (Prince of Wales Hospital; Man et al., 2007). The characteristics of the cases are summarized in Table S1. AEDs were prescribed for the treatment of epilepsy in 31 cases, neuropathic pain and psychiatric illnesses in 5 cases each, and other indications in the remaining 14. Owing to poor DNA quality in one patient (with CBZ-SJS/TEN), genotyping results for 54 cases were available for analysis. Two hundred seventy-five patients who had taken matching AEDs without developing cADRs served as controls. Their mean age was 44.1 years (range 10–90; SD 16.9), and 154 (56.0%) were female.

Association between HLA-B*15:02 and AED-SJS/TEN

HLA-B genotypes of the individual cases and controls are listed in Tables S2 and S3, respectively. A total of 106 different HLA-B alleles were detected among all the subjects, of which 11 were present in at least 3% of controls. Among the cases, the most common alleles were HLA-B*15:02 (carrier rate 63%), HLA-B*13:01 (20.4%), and HLA-B*38:02 and HLA-B*46:01 (both 14.8%). Among the controls, the most common alleles were HLA-B*46:01 (25.5%), HLA-B*40:01 (24%), HLA-B*58:01 (18.9%), and HLA-B*15:02 (15.3%). Collectively, the carrier rate of HLA-B*15:02 was significantly higher in AED-SJS/TEN cases (63.0% [34/54]) compared with AED-tolerant controls (15.3% [42/275]; $p = 2.92 \times 10^{-14}$; OR 9.43; 95% CI 4.96–17.93; Table 1). The carrier rate of HLA-B*15:02 in the controls was similar to that reported in the general Hong Kong Han Chinese population (19.8%; Middleton et al., 2004). When the carrier rates for the individual AEDs were analyzed, this difference between cases and controls appeared largely driven by CBZ. Therefore, the carrier rate of HLA-B*15:02 in CBZ-SJS/TEN cases (92.3% [24/26]) was significantly higher than that in CBZ-tolerant controls (11.9% [16/135]; $p = 3.51 \times 10^{-18}$; OR 89.25; 95% CI 19.25–413.83), with sensitivity of 92.3% (95% CI 75.9–97.9) and specificity of 88.1% (95% CI 81.6–92.6). The two patients with CBZ-SJS/TEN who did not carry HLA-B*15:02 had HLA-B*13:01/B*54:01 and HLA-B*13:01/B*15:01, respectively (Table S2).

There was a trend of higher carrier rate of HLA-B*15:02 in PHT-SJS/TEN cases (46.7% [7/15]) compared with PHT-tolerant controls (15/75 [20.0%]; $p = 0.045$; OR 3.50; 95% CI 1.10–11.18), with sensitivity of 46.7% (95% CI 24.8–69.9) and specificity of 80.0% (95% CI 69.6–87.5). There was no difference in HLA-B*15:02 carrier rate between the few cases of SJS/TEN induced by LTG, VPA, or PB and their respective drug-tolerant controls. The single cases of SJS/TEN induced by GBP and LEV were both negative for HLA-B*15:02 (Table 1).

Meta-analysis of association between HLA-B*15:02 and PHT- or LTG-SJS/TEN

A total of 103 PHT-related articles were identified. The following articles were excluded: 21 duplicated studies; 59 review articles, commentary, expert opinion, and editorial articles; 12 non-PHT-HLA-B*15:02 association studies; 2 non-Chinese studies; one conference abstract; 5 case reports or studies with no drug-tolerant control; one non-SJS/TEN report; and one overlapping data with present study. Finally, one article was included in the meta-analysis together with the present study. No additional suitable article was selected from reviewing the references of the selected articles.

Table 1. Carrier rates of HLA-B*15:02 in cases with antiepileptic drug–induced Stevens-Johnson syndrome/toxic epidermal necrolysis and in drug-tolerant controls

	No. of HLA-B*15:02 carriers/Total no. in group (%)			
Drug	Cases	Controls	p-Value[a]	OR (95% CI)
All AEDs[b]	34/54 (63.0)	42/275 (15.3)	2.92×10^{-14}	9.43 (4.96–17.93)
CBZ	24/26 (92.3)	16/135 (11.9)	3.51×10^{-18}	89.25 (19.25–413.83)
PHT	7/15 (46.7)	15/75 (20.0)	0.045	3.50 (1.10–11.18)
LTG	2/6 (33.3)	4/30 (13.3)	0.256	3.25 (0.44–23.95)
VPA	1/3 (33.3)	4/15 (26.7)	1.000	1.38 (0.10–19.64)
PB	0/2 (0)	2/10 (20.0)	1.000	–
GBP	0/1 (0)	0/5 (0)	–	–
LEV	0/1 (0)	1/5 (20.0)	–	–

AED, antiepileptic drug; CBZ, carbamazepine; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OR, odds ratio; PB, phenobarbital; PHT, phenytoin; VPA, sodium valproate.

[a]Unadjusted p-values. $p < 0.01$ (0.05/5) considered to be significant after adjustment for multiple comparisons of five individual drugs using Bonferroni's correction. Drug specific comparison was not performed for gabapentin (GBP) and levetiracetam (LEV) owing to single cases.

[b]All antiepileptic drugs combined.

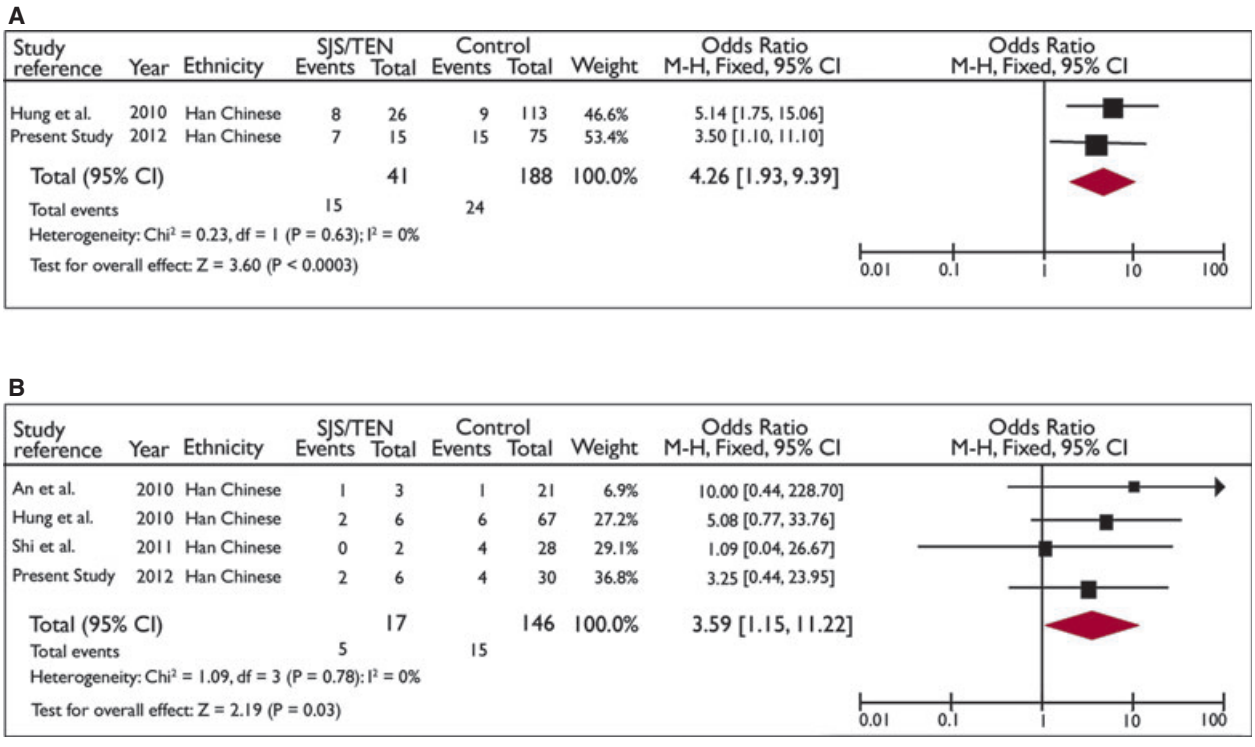

Figure 1.

Forest plots showing associations of HLA-B*15:02 with phenytoin- and lamotrigine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Asians. Different studies matching the selection criteria for association of HLA-B*15:02 with phenytoin- (**A**) and lamotrigine- (**B**) induced Stevens-Johnson syndrome/toxic epidermal necrolysis were grouped for meta-analyses in a fixed-effect model using Mantel-Haenszel statistics. Pooled odds ratios are demonstrated by diamonds with the width showing 95% confidence intervals. Study weighting is indicated by different sizes of squares with the horizontal lines showing 95% confidence intervals. The analyses were tested for heterogeneity using chi-square and I-square test. The overall effects were calculated by combined z-values with $p < 0.05$ indicating statistical significance. d.f., degrees of freedom; M-H, Mantel-Haenszel; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Meta-analysis of these two studies in Taiwan (Hung et al., 2010) and Hong Kong (present study), comprising in total 41 cases and 188 controls, showed positive association of HLA-B*15:02 with PHT-SJS/TEN ($p < 3 \times 10^{-4}$; OR 4.26; 95% CI 1.93–9.39) under a fixed-effect model with statistically insignificant heterogeneity (Fig. 1A). By pooling data directly, the association had a sensitivity of 36.6% (95% CI 23.6–51.9) and specificity of 87.2% (95% CI 81.7–91.3).

A total of 77 LTG-related articles were retrieved. The following articles were excluded: 9 duplicated studies; 50 review articles, commentary, expert opinion and editorial articles; 8 non-LTG-HLA-B*15:02 association studies; 3 non-Chinese studies; 2 conference abstracts; one study with no drug-tolerant control; and one overlapping data with present study. Finally, three articles were included in the meta-analysis together with the present study. No additional suitable article was selected from reviewing the references of the selected articles.

Meta-analysis of these four studies from mainland China (An et al., 2010; Shi et al., 2011), Taiwan (Hung et al., 2010), and Hong Kong (present study), comprising in total 17 cases and 146 controls, showed positive association of HLA-B*15:02 with LTG-SJS/TEN (p = 0.03; OR 3.59; 95% CI 1.15–11.22) under a fixed-effect model with statistically insignificant heterogeneity (Fig. 1B). By pooling data directly, the association had a sensitivity of 29.4% (95% CI 13.3–53.1) and specificity of 89.7% (95% CI 83.7–93.7).

Association with other common HLA-B alleles

We analyzed whether there were other common HLA-B alleles associated with AED-SJS/TEN. When comparing all AEDs collectively, HLA-B*58:01 and HLA-B*40:01 were negatively associated with AED-SJS/TEN (p = 0.006 and p = 0.036, respectively; Table 2). These alleles were further tested in CBZ cases and non-CBZ cases with their matching controls separately. The carrier rate of HLA-B*40:01 was lower in CBZ-SJS/TEN cases compared with CBZ-tolerant controls (3.8% [1/26] vs. 31.1% [42/135]; p = 0.004; OR 0.09; 95% CI 0.01–0.68). The carrier rate of HLA-B*58:01 was also slightly lower in the former group (7.7% [2/26] vs. 19.3% [26/135]; p = 0.256; OR 0.35; 95% CI 0.08–1.57). None of the cases with SJS/TEN induced by non-CBZ AEDs carried HLA-B*58:01 (0/28) compared with 18.6% (26/140) in matched AED-tolerant controls (p = 0.009). The carrier rate of HLA-B*40:01 was similar between non-CBZ-SJS/TEN cases and their matching controls (17.9% [5/28] vs. 17.1% [24/140]). The carrier rates of HLA-B*58:01 and HLA-B*40:01 in the AED-tolerant controls were similar to those reported in the general Han Chinese population in Hong Kong (14.2% and 28.0%, respectively; Middleton et al., 2004).

Discussion

Through determining the actual HLA-B genotypes, we confirmed our previous report on a smaller sample (Man et al., 2007) that the HLA-B*15:02 allele was associated with AED-SJS/TEN among Han Chinese in Hong Kong. Upon drug-specific analysis, the association was largely attributable to the strong association with CBZ-SJS/TEN, consistent with studies conducted in Taiwan (Chung et al., 2004; Hung et al., 2006) and mainland China that also included Han Chinese (Wang et al., 2011), as well as in Southeast Asian regions, such as Malaysia (Chang et al., 2011; Then et al., 2011) and Thailand (Locharernkul et al., 2008; Tassaneeyakul et al., 2010). Given the high carrier rate of HLA-B*15:02 in the native ethnic groups in these areas (up to 20%), our results provide further support to the recognition of the allele as a valid pharmacogenomic biomarker by the US Food and Drug Administration (2012), as reflected in the updated drug label that people with ancestry

Table 2. Carrier rates of common HLA-B alleles (carrier rate at least 3% in controls; other than HLA-B*15:02) in cases with antiepileptic drug–induced Stevens-Johnson syndrome/toxic epidermal necrolysis and in drug-tolerant controls

	No. of HLA-B allele variant carriers (%)			
HLA-B allele[a]	Cases (n = 55)	Controls (n = 275)	p-Value[b]	OR (95% CI)
B*13:01	11 (20.4)	34 (12.4)	0.117	1.81 (0.85–3.85)
B*15:01	3 (5.6)	11 (4.0)	0.710	1.41 (0.38–5.24)
B*38:02	8 (14.8)	31 (11.3)	0.462	1.37 (0.59–3.17)
B*39:01	0 (0.0)	10 (3.6)	0.377	–
B*40:01	6 (11.1)	66 (24.0)	0.036	0.40 (0.16–0.97)
B*46:01	8 (14.8)	70 (25.5)	0.093	0.51 (0.23–1.13)
B*51:01	3 (5.6)	9 (3.3)	0.424	1.74 (0.46–6.64)
B*54:01	1 (1.9)	10 (3.6)	1.000	0.50 (0.06–3.99)
B*55:02	1 (1.9)	14 (5.1)	0.480	0.35 (0.05–2.73)
B*58:01	2 (3.7)	52 (18.9)	0.006	0.17 (0.04–0.70)

OR, odds ratio.
[a]Only carrier rate >3% in the control are shown.
[b]Unadjusted p-values. $p < 0.005$ (0.05/10) considered to be significant after adjustment for multiple comparisons of 10 alleles using Bonferroni's correction.

in these at-risk populations should be tested for the allele before starting CBZ, which should be avoided in individuals who test positive (Novartis, 2010).

Cross-reactivity in cADRs is common among the aromatic AEDs (CBZ, LTG, oxcarbazepine, PB, PHT; Alvestad et al., 2008). Association between HLA-B*15:02 and PHT-SJS/TEN has been suggested in several studies conducted in Chinese and Thai populations (Locharernkul et al., 2008; Hung et al., 2010; Min et al., 2011; Wang et al., 2012) although not in a case report (Hu et al., 2011). A possible trend of association between the allele and SJS/TEN induced by LTG in Han Chinese has been suggested in two studies (An et al., 2010; Hung et al., 2010) but not in another (Shi et al., 2011). These trends were also observed in the present study. Individually, these previous and the present studies are limited in their ability to draw firm conclusions owing to their relatively small sample sizes. However, meta-analyses of the studies in Han Chinese (Fig. 1) showed that HLA-B*15:02 is associated with PHT-SJS/TEN ($p < 3 \times 10^{-4}$), consistent with findings in the Thai population (Locharernkul et al., 2008). Although marginally significant ($p = 0.03$), because the pooled sample size is still limited, the association between HLA-B*15:02 and LTG-SJS/TEN remains to be confirmed in larger studies. Recent in vitro studies of CBZ and its structural analogs suggest that the 5-carboxamide group is critical for the interaction of CBZ with HLA-B*15:02 and the stimulation of T cells, with the binding affinity determined by modification of the chemical ring structure (Wei et al., 2012). Although they have aromatic ring structures, PHT, LTG, and PB do not possess the carboxamide moiety, whereas VPA, GBP, and LEV are not aromatic compounds. These structural differences might account for the difference among AEDs in association between HLA-B*15:02 and severe cADRs.

Apart from HLA-B*15:02, other members of HLA-B75 serotype have been implicated for CBZ-SJS/TEN, such as HLA-B*15:08 in Indians (Mehta et al., 2009), HLA-B*15:11 in Japanese and Han Chinese (Kaniwa et al., 2008, 2010; Shi et al., 2012), HLA-B*15:18 in Japanese (Ikeda et al., 2010), and HLA-B*15:21 in Thai (Tassaneeyakul et al., 2010). The rationale is that their similar amino acid sequence homology may resemble structural features of HLA-B*15:02 and thus may be able to trigger a similar cADR to CBZ (Wei et al., 2012). In the present study, we found no carrier of these types except one CBZ-tolerant control carrying HLA-B*15:21 (Table S2), although these HLA alleles are generally uncommon (0.0–1.1% carrier rate) in the Hong Kong Chinese population (Middleton et al., 2004).

Several studies have suggested that certain HLA alleles may exert a protective effect against CBZ-SJS/TEN, as evidenced by lower carrier frequencies in cases compared with CBZ-tolerant controls, including HLA-B*40:01 in Taiwan Han Chinese (Hung et al., 2006) and HLA-B*07:02 in Caucasians (Alfirevic et al., 2006). Consistent with the report from Taiwan (Hung et al., 2006), lower carrier rate of HLA-B*40:01 was noted in CBZ-cADR cases in the present study compared with CBZ-tolerant controls. Of interest, the carrier rate of HLA-B*58:01, which is associated with allopurinol-SJS/TEN (Hung et al., 2005), was lower in cases with SJS/TEN induced by AEDs other than CBZ ($p = 0.009$). Notably, none of the cases had the allele compared with 18.6% in the drug tolerant controls, similar to the local general population. The difference did not reach statistical significance after correction for multiple comparisons, probably due to the small sample size.

The possibility that an HLA allele may exert an increased risk of severe cADRs induced by one medication but decrease the risk of the same phenotype related to other drugs is intriguing. Recent systematic comparison of genome-wide association studies has shown that alleles of genes involved in antigen presentation, Th1/Th2 balance, and the inflammation process can have opposite genetic association direction between asthma and autoimmune diseases (Li et al., 2012). Advances in the understanding of the mechanisms of the association between HLA alleles and severe cADRs may shed further light in demonstrating that direct binding of the drug to the HLA molecule led to changes in the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and driving T-cell activation (Illing et al., 2012). It might be conceivable that the same HLA molecule interacts differently with different drugs, thus resulting in different effects on the peptide repertoire downstream. This finding also suggests that factors other than HLA genotype may be involved in the pathogenesis of severe cADRs. Indeed, preferred T-cell receptor (TCR) clonotypes have been recently found in different CBZ-SJS/TEN individuals demonstrating the essential role of TCR in pathogenic mechanism of severe cADRs in addition to HLA molecule, peptide, and drug (Ko et al., 2011). It would be worthwhile to study whether the same or different TCR clonotypes would be identified in SJS/TEN induced by other drugs, such as allopurinol and PHT.

Recently, genome-wide association studies conducted in European Caucasians (McCormack et al., 2011) and Japanese (Ozeki et al., 2011) have identified an association between the broad range of various CBZ-cADRs and the single nucleotide polymorphism rs1061235, a reported proxy for HLA-A*31:01, although the earlier report in Taiwan Han Chinese observed a modest association ($p = 1.3 \times 10^{-4}$) of the allele with the milder MPE only and not with SJS/TEN or HSS induced by CBZ (Hung et al., 2006). We, therefore, did not include the allele in the present analysis that focused on SJS/TEN and the HLA-B locus, which has been implicated in cADRs induced by multiple medications.

In conclusion, we confirmed the strong association between HLA-B*15:02 and CBZ-SJS/TEN in Hong Kong

Han Chinese. The meta-analysis with previous studies confirmed a clinically relevant association between the allele and PHT-SJS/TEN, supporting the FDA recommendation that health care providers should *consider* avoiding PHT and its prodrug, fosphenytoin, as alternatives for CBZ in HLA-B*15:02 carriers (U.S. Food & Drug Administration, 2008). Possible protective association of HLA-B*40:01 with CBZ-SJS/TEN and of HLA-B*58:01 with non-CBZ-SJS/TEN warrant further investigation.

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Disclosure

PK has provided consultancy to Eisai, GSK, Pfizer, and UCB Pharma; received research support from Eisai, Johnson & Johnson, Pfizer, and UCB Pharma; and lectured in speakers' bureaus of Eisai and UCB Pharma. All other authors have no conflict of interest to declare. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of characteristics of cases with antiepileptic drug–induced Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table S2. Characteristics of patients with antiepileptic drug–induced Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table S3. Characteristics and HLA-B genotypes of drug-tolerant controls.