HLA-A*24:02 as a common risk factor for antiepileptic drug–induced cutaneous adverse reactions

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ABSTRACT

Objective: To investigate the involvement of human leukocyte antigen (HLA) loci in aromatic antiepileptic drug–induced cutaneous adverse reactions.

Methods: A case-control study was performed to detect HLA loci involved in aromatic antiepileptic drug–induced Stevens-Johnson syndrome in a southern Han Chinese population. Between January 1, 2006, and December 31, 2015, 91 cases of Stevens-Johnson syndrome induced by aromatic antiepileptic drugs and 322 matched drug-tolerant controls were enrolled from 8 centers. Important genotypes were replicated in cases with maculopapular eruption and in the meta-analyses of data from other populations. Sequence-based typing determined the HLA-A, HLA-B, HLA-C, and HLA-DRB1 genotypes.

Results: HLA-B*15:02 was confirmed as strongly associated with carbamazepine-induced Stevens-Johnson syndrome ($p = 5.63 \times 10^{-15}$). In addition, HLA-A*24:02 was associated significantly with Stevens-Johnson syndrome induced by the aromatic antiepileptic drugs as a group ($p = 1.02 \times 10^{-5}$) and by individual drugs (carbamazepine $p = 0.015$, lamotrigine $p = 0.005$, phenytoin $p = 0.027$). Logistic regression analysis revealed a multiplicative interaction between HLA-B*15:02 and HLA-A*24:02. Positivity for HLA-A*24:02 and/or HLA-B*15:02 showed a sensitivity of 72.5% and a specificity of 69.0%. The presence of HLA-A*24:02 in cases with maculopapular exanthema was also significantly higher than in controls ($p = 0.023$). Meta-analysis of data from Japan, Korea, Malaysia, Mexico, Norway, and China revealed a similar association.

Conclusions: HLA-A*24:02 is a common genetic risk factor for cutaneous adverse reactions induced by aromatic antiepileptic drugs in the southern Han Chinese and possibly other ethnic populations. Pretreatment screening is recommended for people in southern China. ***Neurology*®** **2017;88:2183–2191**

GLOSSARY

AED = antiepileptic drug; **cADR** = cutaneous adverse drug reaction; **CBZ** = carbamazepine; **HLA** = human leukocyte antigen; **LTG** = lamotrigine; **MPE** = maculopapular exanthema; **PHT** = phenytoin; **SJS** = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.

皮肤药物不良反应（cADRs）包括：轻微斑丘疹性皮疹和严重的皮肤反应，如超敏反应综合征、Stevens-Johnson综合征（SJS）、和中毒性表皮坏死松解症（TEN）

Cutaneous adverse drug reactions (cADRs) include mild maculopapular exanthema (MPE) and severe cutaneous reactions such as hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).[1] cADRs are considered a major public health issue because of their potentially life-threatening morbidity, especially severe cutaneous reactions. The incidence of SJS/TEN is estimated to vary from 1 in 1,000 to 10,000 drug exposures,[2,3] and its mortality is as high as 35%.[4,5] Many drugs are associated with cADRs; however, the majority of severe cutaneous reactions cases are caused by a few drug classes.[6] Antiepileptic drugs (AEDs), particularly those with aromatic ring structures such as carbamazepine (CBZ), lamotrigine (LTG), and phenytoin (PHT), are among the most common

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抗癫痫药物引起的SJS约0.2%，均由服用芳香族抗癫痫药物引起。

人类白细胞抗原标志物已证实与药物引发的皮肤药物不良反应相关
HLA-B 5701与阿巴卡韦引发的超敏反应相关
HLA-B 5801与别嘌呤醇引发的SJS/TEN相关
HLA-B 1502 是高风险的基因标志物，与台湾服用卡马西平的汉族人群发生SJS/TEN相关
这个结果在南方的中国汉族和东南亚人群得以印证，在预防卡马西平引发SJS/TEN获得重大突破

causes of severe cutaneous reactions.[1,7] The incidence of AED-induced SJS was estimated as 0.2%, and all cases occurred in individuals receiving aromatic AEDs.[8]

Several human leukocyte antigen (HLA) markers have been identified for drug-induced cADRs. HLA-B*57:01 was associated with abacavir-induced hypersensitivity reaction.[9,10] HLA-B*58:01 was associated with allopurinol-induced SJS/TEN.[11] HLA-B*15:02 is a high-risk genetic marker for CBZ-induced SJS/TEN in Han Chinese individuals living in Taiwan.[12] This finding was confirmed in southern Han Chinese[13,14] and populations in southeast Asia[15–17] and has resulted in breakthroughs in the prevention of CBZ-induced SJS/TEN.[18] Subsequently, cases of CBZ-induced SJS/TEN that were negative for HLA-B*15:02 in Chinese,[19,20] Indian, Thai, and Malay populations were reported.[15–17] In our extended study, we revealed a potential association between HLA-A*24:02 and CBZ-induced SJS/TEN in a southern Han Chinese population.[14,21] These findings suggested that in addition to HLA-B*15:02, other genetic factors might contribute to CBZ-induced SJS/TEN. The relationships between HLA genes and the other commonly used aromatic AEDs, including LTG and PHT, are unclear.

To examine the HLA loci involved in aromatic AED–induced SJS, we conducted a multicenter case-control study in southern China. Significant findings were replicated in MPE cases and validated with meta-analyses of data from independent studies in other populations.

METHODS

Recruitment of cases and drug-tolerant controls. Cases included individuals who developed cADRs after receiving aromatic AEDs. The Roujeau diagnostic criteria were used to diagnose and classify cADRs,[5,22] and a dermatologist confirmed the diagnoses on the basis of the clinical morphology of the skin damage. SJS is defined as mucocutaneous disorders characterized by extensive erythema, blisters, epidermal detachment, enanthema, and skin detachment of <10% of the body surface area. TEN is defined as skin detachment >30%. The SJS-TEN overlap is defined as skin detachment of 10% to 30%. MPE is characterized by cutaneous fine pink macules and papules, and lesions without mucosal or systemic involvement. Cases were defined as participants who developed cADRs within 8 weeks of beginning an aromatic AED for which no other causes were found. No cases were taking other medicines associated with SJS/TEN such as abacavir and allopurinol.

We recruited cases between 2006 and 2015 from 8 hospitals in 4 regions in southern China, including Guangdong, Hong Kong, Hubei, and Sichuan. As a part of the follow-up after AEDs were prescribed, individuals were asked to return to the hospital if they developed cADRs. Controls were participants with epilepsy who took aromatic AEDs for at least 3 months without evidence of cutaneous adverse reactions. To determine whether the association between HLA and cADRs was drug-specific and ethnicity-specific, controls were Han Chinese from the same region who took the same AEDs as the matched cases. A matching ratio of at least 3:1 (controls:cases) was used.

To replicate any significant findings, a cohort of MPE cases was recruited separately from 2007 to 2015 in Guangzhou, Guangdong province.

All individuals enrolled were unrelated ethnic Han Chinese. None of the biological grandparents of the participants were from other races.

HLA high-resolution genotyping. We extracted genomic DNA from peripheral blood using the QIARamp blood mini-kit (Qiagen, Hilden, Germany). The Shanghai Tissuebank Biotechnology (Shanghai, China) performed the high-resolution sequence-based HLA typing. An ABI 3730 sequencer (Applied Biosystems, Foster City, CA) was used to perform the sequencing for HLA genotyping. The primers used for PCR amplification of DNA fragments of the HLA-A, HLA-B, HLA-C, and HLA-DRB1 genes were as follows: (1) AF and AR for HLA-A alleles, (2) BF and BR for HLA-B alleles, (3) CF and CR for HLA-C alleles, and (4) DRB1F and DRB1R for HLA-DRB1 alleles (table e-1 at Neurology.org). The primers used for resequencing of the HLA-A, HLA-B, HLA-C, and HLA-DRB1 genes are also listed in table e-1. Sequence alignment was used to determine the 4-digit HLA alleles with the software vector NTI 6.0 (Informax Inc, Gaithersburg, MD).

Meta-analysis. To validate the findings from the present cohort, we performed meta-analyses on data obtained from other populations. A complete search of online databases, including MEDLINE, EMBASE, Google Scholar, the Chinese National Knowledge Infrastructure, and the China Science and Technology Journal, were conducted. Detailed information regarding the search method and criteria of selection and exclusion is presented in the e-supplement. Data from 14 studies were used for the meta-analyses. These studies included populations from Japan, Korea, Malaysia, Mexico, Norway, and China.

Standard protocol approvals, registrations, and patient consents. The studies adhered to the guidelines of the International Committee of Medical Journal Editors with regard to patient consent for research or participation and received approval from local ethics committees of the participating hospitals.

The Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University provided ethics approval.

Statistical analysis. SPSS version 19.0 (SPSS Inc, Chicago, IL) was used to perform the statistical analyses. Two-by-two χ^2 tests were performed to compare the allele carrier rates between groups. Logistic regression was used to analyze the possible interaction between HLA-A*24:02 and HLA-B*15:02.Values of $p < 0.05$ (2-sided) were considered statistically significant. Bonferroni correction for p values was applied when multiple comparisons were performed (e-supplement).

RESULTS

HLA and SJS/TEN. ***Overall findings.*** Ninety-one cases with aromatic AED–induced SJS/TEN (56 CBZ-SJS/TEN, 22 LTG-SJS, and 13 PHT-SJS) and 322 controls (180 exposed to CBZ, 102 to LTG, and 40 to PHT) were included. Table e-2 summarizes the

demographic variables of the cases and controls. There were no significant differences between the case and control groups in mean age, sex ratio, and the presence of major comorbidities. As expected, the CBZ and LTG controls showed significantly higher exposure doses than the cases. Similarly, the controls showed a higher rate of concomitant aromatic AED use. Most cases received aromatic AEDs to treat epilepsy, except for 9 patients who received AEDs to treat neuropathies (6 cases), psychiatric illness (1 case), blepharospasm (1 case), and postoperation prophylaxis (1 case). For the 9 individuals with nonepileptic indications, we failed to find matching controls with the same indications. Because of the possible risk of bias, 2 situations, i.e., with or without cases without epilepsy, were considered separately in the statistical analysis. There was no difference in the results of the statistical analysis between the 2 scenarios.

The genotypes of HLA-A, HLA-B, HLA-C, and HLA-DRB1 in the 91 cases with CBZ-, LTG-, and PHT-induced SJS/TEN are shown in table e-3. HLA alleles that are associated significantly with cADRs from the 2-by-2 χ^2 analyses are listed in table 1, while comparisons of all alleles are shown in table e-4.

As shown in table 1, 6 alleles were detected as significant in the CBZ-induced SJS/TEN group: HLA-B*15:02, HLA-C*08:01, HLA-DRB1*12:02, HLA-A*24:02, HLA-B*15:11, and HLA-DRB1*01:01. The HLA-C*08:01 and HLA-DRB1*12:02 alleles are recognized as haplotype alleles of HLA-B*15:02,[23] appearing with HLA-B*15:02 in 90.6% (48 of 53) and 81.6% (31 of 38) of cases, respectively (table e-5). HLA-B*15:11 and HLA-DRB1*01:01 appeared with HLA-B*15:02 and/or HLA-A*24:02 in all but 1 case each (table e-6). Thus, HLA-B*15:02 and HLA-A*24:02

Table 1 Risk factors for CBZ-, LTG-, and PHT-induced SJS/TEN

	HLA genotypes/total, n/N (%)		Cases vs controls	
Allele	SJS/TEN[a]	Controls[a]	*p* Value	OR (95% CI)
CBZ				
B*15:02	39/56 (69.64)	28/179 (15.64)	5.63×10^{-15}[b]	12.37 (6.16–24.86)
C*08:01[c]	42/55 (76.36)	38/177 (21.47)	7.36×10^{-14}	11.82 (5.76–24.23)
DRB1*12:02[c]	29/54 (53.7)	45/176 (25.57)	1.08×10^{-4}	3.38 (1.79–6.36)
A*24:02	17/56 (30.36)	28/178 (15.73)	0.015	2.33 (1.16–4.69)
B*15:11[d]	4/56 (7.14)	0/179 (0)	0.003	30.77 (1.63–580.87)
DRB1*01:01[d]	4/54 (7.41)	1/176 (0.57)	0.013	14.0 (1.53–128.10)
LTG				
A*24:02	10/22 (45.45)	16/102 (15.69)	0.005[b]	4.48 (1.66–12.11)
PHT				
A*24:02	6/13 (46.2)	5/40 (12.5)	0.027	6.00 (1.42–25.27)
A*02:01[d]	3/13 (23.1)	1/40 (2.5)	0.042	11.7 (1.10–124.84)
Pooled				
B*15:02	50/91 (54.95)	56/321 (17.45)	5.07×10^{-13}[b,e]	5.77 (3.49–9.55)
C*08:01[c]	53/88 (60.23)	73/319 (22.88)	1.97×10^{-11}	5.10 (3.09–8.42)
DRB1*12:02[c]	38/87 (43.68)	81/317 (25.55)	0.001	2.26 (1.38–3.70)
A*24:02	33/91 (36.26)	49/320 (15.31)	1.02×10^{-5}[b,e]	3.15 (1.86–5.32)
B*15:11[d]	4/91 (4.40)	2/321 (0.62)	0.031	7.33 (1.32–40.7)
B*15:01	8/91 (8.79)	9/321 (2.80)	0.025	3.34 (1.25–8.93)

Abbreviations: CBZ = carbamazepine; CI = confidence interval; HLA = human leukocyte antigen; LTG = lamotrigine; OR = odds ratio; PHT = phenytoin; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.
[a] Several individuals were not subjected to HLA genotyping because of insufficient DNA.
[b] Significant after Bonferroni correction (e-supplement and table e-4), $p = 1.35 \times 10^{-13}$, n = 24 for HLA-B*15:02 correction in CBZ-SJS; $p = 0.04$, n = 8 for HLA-A*24:02 correction in LTG-SJS; $p = 1.93 \times 10^{-11}$, n = 38 for HLA-B*15:02 correction in SJS pooled data; and $p = 1.43 \times 10^{-4}$, n = 14 for HLA-A*24:02 correction in SJS pooled data.
[c] The haplotype allele of HLA-B*15:02.
[d] These alleles appeared with HLA-B*15:02 or HLA-A*24:02 in all but 1 or 2 cases each.
[e] When the 9 cases without epilepsy were excluded, $p = 6.74 \times 10^{-13}$, OR 6.05 (95% CI 3.59–10.20) for HLA-B*15:02; and $p = 5.33 \times 10^{-6}$, OR 3.36 (95% CI 1.96–5.77) for HLA-A*24:02. $p = 2.56 \times 10^{-11}$ for HLA-B*15:02 and $p = 7.46 \times 10^{-5}$ for HLA-A*24:02 after Bonferroni correction.

remained the only significantly associated alleles. HLA-A*24:02 was a significantly associated allele in patients who were negative for HLA-B*15:02 (7 of 17 vs 24 of 149 in CBZ controls, odds ratio 3.65, 95% confidence interval 1.26–10.52, $p = 0.029$). HLA-B*15:02/HLA-A*24:02 is not a common haplotype in southern Han Chinese (http://www.allelefrequencies.net).[23,24] These data suggested that the HLA-A*24:02 allele is independently and significantly associated with CBZ-induced SJS/TEN.

In the LTG-induced SJS group, HLA-A*24:02 was the only significantly associated allele detected.

In the PHT-induced SJS group, in addition to HLA-A*24:02, HLA-A*02:01 was found to be marginally significantly associated but appeared alone in only 2 cases.

In the pooled analysis (table 1), HLA-B*15:02 and HLA-A*24:02 appeared to be associated alleles ($p = 5.07 \times 10^{-13}$ and $p = 1.02 \times 10^{-5}$, respectively), and remained significant after Bonferroni correction ($p = 1.93 \times 10^{-11}$ and $p = 1.43 \times 10^{-4}$, respectively, table e-2). In addition, HLA-B*15:11 and HLA-B*15:01 were potentially associated alleles.

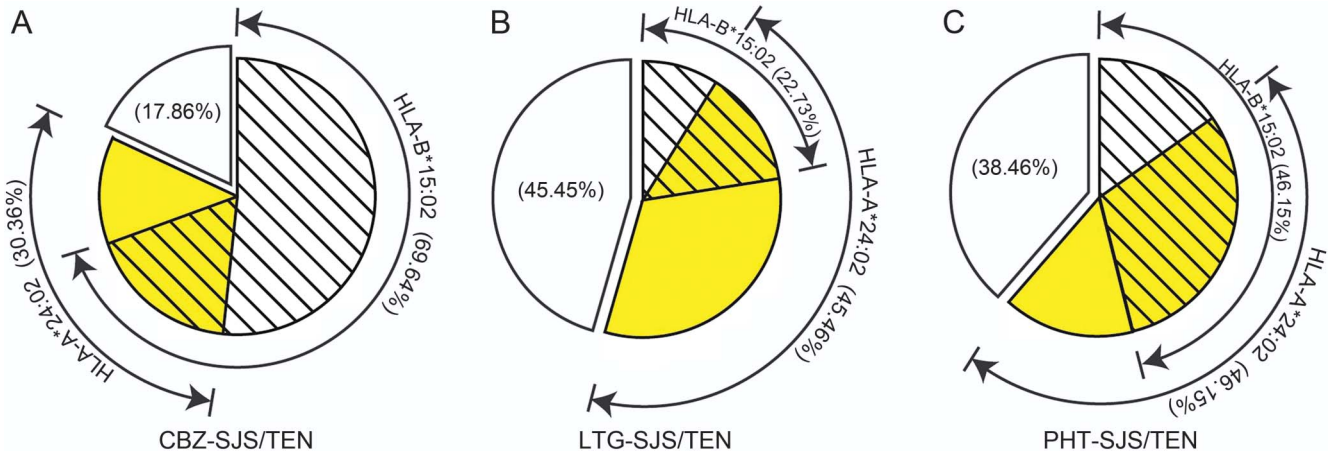
HLA-B*15:02. The carrier rate of HLA-B*15:02 was higher in the CBZ-induced SJS/TEN group compared with the control group ($p = 5.63 \times 10^{-15}$). HLA-B*15:02 showed a sensitivity of 69.6% and specificity of 84.4% for CBZ-induced SJS/TEN. HLA-B*15:02 was present in 22.7% (5 of 22) of cases with LTG-induced SJS, 18.6% (19 of 102) of LTG controls ($p = 0.89$), 46.2% (6 of 13) of cases with PHT-SJS, and 22.5% (9 of 40) of PHT controls ($p = 0.22$). These findings suggested that HLA-B*15:02 is a high-risk but relatively specific factor for CBZ-induced SJS/TEN.

HLA-A*24:02. HLA-A*24:02 was present in 30.4% (17 of 56) of patients with CBZ-induced SJS/TEN, which was more frequent than in CBZ controls (28 of 178, 15.7%, $p = 0.015$). In the LTG-induced SJS group, 45.4% (10 of 22) of cases carried HLA-A*24:02, which was more frequent than in the LTG controls ($p = 0.005$, $p = 0.04$ after Bonferroni correction) (table e-2). Similarly, a significant difference was found for the presence of HLA-A*24:02 between cases with PHT-induced SJS and PHT controls (6/13 vs 5/40, $p = 0.027$). These findings suggested that HLA-A*24:02 is a potential shared risk factor for CBZ-, LTG-, and PHT-induced SJS/TEN. The sensitivity and specificity were 30.4% and 84.3% for CBZ, 45.4% and 84.3% for LTG, and 46.2% and 87.5% for PHT, respectively.

Interaction between HLA-B and HLA-A. HLA-B*15:02 and HLA-A*24:02 were present either alone or together in patients with AED-induced SJS/TEN (figure 1). Thus, we performed logistic regression analyses to examine the potential interaction between the 2 alleles (table 2). The odds ratios in SJS/TEN patients who were positive for both HLA-B*15:02 and HLA-A*24:02 were higher than in those patients who were positive for either HLA-B*15:02 or HLA-A*24:02 alone. A potential multiplicative interaction between HLA-B*15:02 and HLA-A*24:02 was observed (odds ratio 1.31). The estimated excess risk from the interaction was 16.85. Combining HLA-A*24:02 and HLA-B*15:02 into a single group (i.e., carriers of HLA-A*24:02 and/or HLA-B*15:02) increased the sensitivity to 82.1% for CBZ-SJS/TEN and 72.5% for the 3 AED-induced SJS/TENs (with specificities 70.6% and 69.0%, respectively).

Additional logistic regression analyses were performed to examine the potential interactions between

Figure 1 Presence of HLA-B*15:02 and HLA-A*24:02 alleles in CBZ- (A), LTG- (B), and PHT- (C) induced SJS/TEN



CBZ = carbamazepine; HLA = human leukocyte antigen; LTG = lamotrigine; PHT = phenytoin; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 2 Excess risk from interaction between HLA-A*24:02 and HLA-B*15:02 alleles in AED-induced SJS/TEN (logistic regression)

HLA-A*24:02	HLA-B*15:02	SJS/TEN, n	Controls, n	OR
+	+	17	6	24.93
+	−	16	43	3.27
−	+	33	50	5.81
−	−	25	220	1.0

Abbreviations: AED = antiepileptic drug; HLA = human leukocyte antigen; OR = odds ratio; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.
With the multiplicative model, the expected joint OR was 19.0 (3.27 × 5.81), and the OR of the multiplicative interaction was 1.31 (24.93/19.00). Under an additive model, the expected joint OR was 8.08 (3.27 + 5.81 − 1), and the excess risk from interaction was 16.85 (24.93 − 8.08).

HLA-B*15:02 or HLA-A*24:02 and each of the other HLA alleles. Potential multiplicative interactions were found between HLA-A*24:02 and HLA-B*15:11 (table e-7) and between HLA-B*15:02 and HLA-A*02:01 (table e-8).

HLA and MPE. Significant genotypes were replicated in 193 cases with MPE recruited in Guangzhou, including 134 with CBZ-induced MPE and 59 with LTG-induced MPE. HLA-A*24:02 was present in 24.2% (45 of 186) of cases with MPE, which was higher than in the controls (15.7%, 44 of 280, $p = 0.023$) (table 3). The frequency of HLA-B*15:02 was similar between the 2 groups ($p = 0.56$).

Meta-analysis. To validate the association between HLA-A*24:02 and aromatic AED–induced cADRs, meta-analysis was performed using data from different populations (e-supplement and tables e-9 and e-10). Two types of data, i.e., from drug-tolerant controls and population controls, were analyzed separately. Compared with the tolerant controls, an association between HLA-A*24:02 and MPE was found in data from Taiwan, Korea, Malaysia, and southern China ($p = 0.046$). There was also an association between HLA-A*24:02 and cADRs for data that did not specify SJS/TEN or MPE, based on data from Japan, Norway, and southern China ($p = 0.031$) (figure 2A). Compared with the population controls, we found an overall association between HLA-A*24:02 and cADRs ($p = 0.036$) (figure 2B) in the data from Japanese, Korean, Mexican, and Chinese populations.

Table 3 Association of HLA-A*24:02 and HLA- B*1502 alleles with CBZ- and LTG-induced MPE

	HLA genotypes/total, n/N (%)		Cases vs controls	
Allele	MPE[a]	Controls[a]	*p* Value	OR (95% CI)
CBZ				
A*24:02	32/131 (24.43)	28/178 (15.73)	0.056	1.73 (0.98–3.05)
B*15:02	19/132 (14.39)	28/179 (15.64)	0.761	0.91 (0.48–1.71)
LTG				
A*24:02	13/55 (23.64)	16/102 (15.69)	0.221	1.66 (0.73–3.78)
B*15:02	9/58 (15.52)	19/102 (18.63)	0.619	0.80 (0.34–1.91)
Pooled				
A*24:02	45/186 (24.19)	44/280 (15.71)	0.023	1.71 (1.08–2.73)
B*15:02	28/190 (14.74)	47/281 (16.73)	0.563	0.86 (0.52–1.43)

Abbreviations: CBZ = carbamazepine; CI = confidence interval; HLA = human leukocyte antigen; LTG = lamotrigine; MPE = maculopapular exanthema; OR = odds ratio.
[a] Several individuals were not tested by HLA genotyping because of insufficient DNA.

DISCUSSION CBZ, LTG, and PHT, which have similar chemical structures and contain an aromatic ring, are prescribed commonly to treat epilepsy,[8,25] which is estimated to affect ≈1% of the world's population.[26] However, these drugs are also among the most common causes of cADRs, especially SJS and TEN.[8,25,27] CBZ-induced SJS/TEN is strongly associated with HLA-B*15:02 in southern Han Chinese[13,14] and populations in southeast Asia with varying sensitivity,[15–17] and CBZ-SJS/TEN is associated with HLA-A*31:01 in whites and Japanese, with sensitivities of 42% and 60.7%, respectively.[28,29] However, HLA markers for LTG- and PHT-induced SJS/TEN have not been established firmly, although a Taiwanese study detected the CYP2C9*3 allele of the drug-metabolizing enzyme in a case of PHT-induced SJS/TEN.[30] In the present study, HLA-A*24:02 was revealed as a shared risk factor for SJS/TEN induced by the aromatic AEDs CBZ, LTG, and PHT, while confirming that HLA-B*15:02 is a high risk factor for CBZ-induced SJS/TEN.

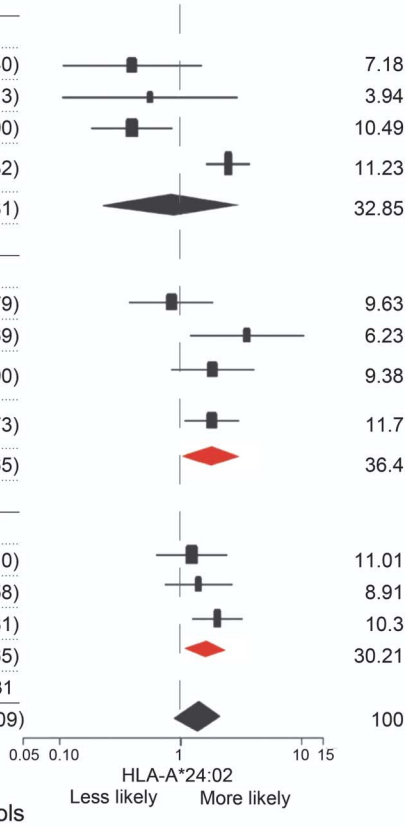
Early studies in Han Chinese living in Taiwan and Hong Kong showed that patients with CBZ-induced SJS/TEN were almost exclusively HLA-B*15:02 carriers.[24,31] Cases of CBZ-induced SJS/TEN were reported in southern Han Chinese who were negative for HLA-B*15:02,[19] with a consistent negative rate of ≈30%. HLA-A*24:02 was also noted as a potential risk factor.[14,21] In the present study, 30.4% of patients with CBZ-induced SJS/TEN were negative for HLA-B*15:02, and HLA-A*24:02 was revealed as a risk factor for CBZ-induced SJS/TEN. The carrier rate of HLA-A*24:02 was higher in patients with CBZ-induced SJS/TEN who were negative for HLA-B*15:02, suggesting that HLA-A*24:02 is an independent risk factor for CBZ-induced SJS/TEN. Furthermore, HLA-A*24:02 was associated with SJS/TEN induced by LTG and PHT, suggesting that HLA-A*24:02 is a common risk factor for aromatic AED–induced SJS/TEN.

HLA-B*15:02 was associated with PHT- or LTG-induced SJS/TEN in Taiwan and Hong Kong Han Chinese.[31–33] We also found a relatively high carrier rate of HLA-B*15:02 in PHT-induced SJS (46.16%)

Figure 2 Distribution of HLA-A*24:02 allele across the phenotypes of cADRs induced by aromatic AEDs

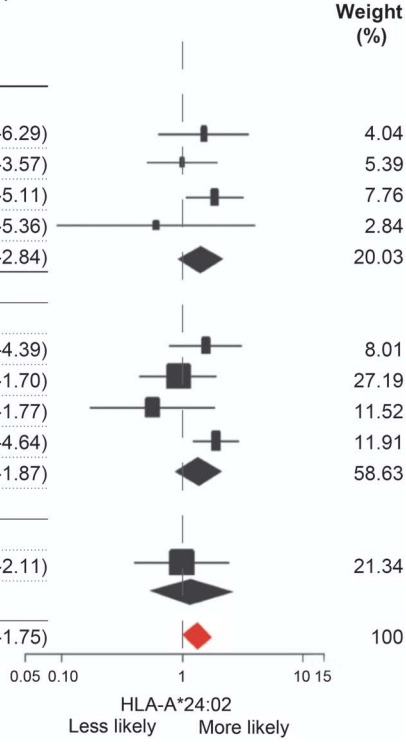
A. Presence of the HLA-A*24:02 allele in AED-induced cADRs and tolerant controls

Subgroup	Cases		Tolerant controls		OR (95% CI)	Weight (%)
	Number HLA-A*24:02 allele carriers	Total number	Number HLA-A*24:02 allele carriers	Total number		
SJS/TEN						
PHT-Taiwan[25]	5	26	37	113	0.49 (0.17-1.40)	7.18
CBZ-Korea[e8]	2	7	21	50	0.55 (0.10-3.13)	3.94
CBZ-Taiwan[26]	18	112	43	152	0.49 (0.26-0.90)	10.49
CBZ/LTG/PHT-Southern China (this study)	33	91	49	320	3.15 (1.86-5.32)	11.23
Subtotal	58	236	150	635	0.85 (0.26-2.81)	32.85
Heterogeneity: Tau^2 =1.2208, chi^2 = 25.05; 3 df, p=0.000; I^2 =88.0%. Test for overall effect: z=0.26; p=0.793						
MPE						
CBZ-Taiwan[26]	13	51	43	152	0.87 (0.42-1.79)	9.63
LTG- Korea[27]	15	21	11	29	4.09 (1.22-13.69)	6.23
CBZ/LTG/PHT-Malaysia (table e-10)	13	30	124	422	1.84 (0.87-3.90)	9.38
CBZ/LTG-Southern China (this study)	45	186	44	280	1.71 (1.08-2.73)	11.7
Subtotal	86	288	222	883	1.63 (1.01-2.65)	36.4
Heterogeneity: Tau^2 =0.1029, chi^2 =5.30; 3 df, p =0.151; I^2 =43.4%. Test for overall effect: z=2.0; p=0.046						
cADRs (Unspecified)						
CBZ-Japan[28]	37	61	211	376	1.21 (0.69-2.10)	11.01
CBZ-Southern China[e12]	16	43	19	70	1.59 (0.71-3.58)	8.91
CBZ/LTG-Norway[29]	24	76	26	169	2.54 (1.34-4.81)	10.3
Subtotal	77	180	256	615	1.67 (1.05-2.65)	30.21
Heterogeneity: Tau^2 =0.0561, chi^2 =2.99; 2 df, p=0.224; I^2 = 33.2%. Test for overall effect: z=2.16; p=0.031						
Total	221	704	628	2133	1.39 (0.93-2.09)	100
Heterogeneity: Tau^2 =0.3121, chi^2 =34.99; 10 df, p=0.000; I^2 =71.4%. Test for overall effect: z=1.59; p=0.112						



B. Frequency of the HLA-A*24:02 allele in AED-induced cADRs and population controls

Subgroup	Cases		Population controls		OR (95% CI)	Weight (%)
	Number HLA-A*24:02 allele carriers	Total number	Number HLA-A*24:02 allele carriers	Total number		
SJS/TEN						
CBZ-Japan[30]	5	10	351	986	1.81 (0.52-6.29)	4.04
CBZ-Korea[e8]	3	14	210	970	0.99 (0.27-3.57)	5.39
CBZ-Southern China[14]	10	32	86	528	2.34 (1.07-5.11)	7.76
LTG-Mexico[e3]	1	8	81	450	0.65 (0.08-5.36)	2.84
Subtotal	19	64	728	2934	1.63 (0.93-2.84)	20.03
Heterogeneity: Tau^2 =0.0000, chi^2 =2.15; 3 df, p=0.541; I^2 =0.0%. Test for overall effect: z=1.71; p=0.087						
MPE						
CBZ-Japan[30]	10	20	351	986	1.81 (0.75-4.39)	8.01
CBZ/LTG-Southern China[e5]	30	166	27	144	0.96 (0.54-1.70)	27.19
CBZ/LTG/PHT-Mexico[e3]	4	34	81	450	0.61 (0.21-1.77)	11.52
LTG-Korea[27]	17	42	210	970	2.46 (1.30-4.64)	11.91
Subtotal	61	262	669	2550	1.31 (0.92-1.87)	58.63
Heterogeneity: Tau^2 =0.2162, chi^2 =7.43; 3 df, p=0.059; I^2 =59.6%. Test for overall effect: z=1.48; p=0.139						
cADRs (unspecified)						
CBZ-Japan[e11]	18	44	281	742	1.14 (0.61-2.11)	21.34
Test for overall effect: z=0.40; p=0.687						
Total	98	370	1678	6226	1.34 (1.02-1.75)	100
Heterogeneity: Tau^2 =0.0577, chi^2 =10.50; 8 df, p=0.232; I^2 =23.8%. Test for overall effect: z=2.09; p=0.036						



Continued

and LTG-induced SJS (22.7%) in the present cohort (figure 1). Thus, we cannot exclude the possibility that HLA-B*15:02 is a risk allele for PTH- or LTG-induced SJS/TEN. Logistic regression analysis revealed an excess risk from the interaction between HLA-A*24:02 and HLA-B*15:02, suggesting that HLA-A*24:02 functions together with HLA-B*15:02 to contribute to aromatic AED–induced SJS/TEN. HLA class I molecules, including HLA-A, HLA-B, and HLA-C, are expressed codominantly on the cell surface. They present peptides to attract killer T cells (also known as $CD8^+$ T cells or cytotoxic T cells) and are involved in the cytotoxic responses in SJS/TEN.[34] Thus, it is plausible that more than one HLA locus is associated with drug-induced SJS/TEN and that their effects might be accumulative, as in the case of HLA-B*15:02 and HLA-A*24:02.

In the replication cohort of MPE cases, HLA-A*24:02 showed an association, suggesting that it also has a role in milder cADRs induced by aromatic AEDs. This was supported by the findings of the meta-analysis of data from independent studies in other populations. An association was found between HLA-A*24:02 and MPE or unspecified cADRs in studies using tolerant controls, and the overall association between HLA-A*24:02 and cADRs in data from studies using population controls was statistically significant. Taken together, these data suggested that HLA-A*24:02 is an independent risk factor for severe SJS/TEN, as well as milder MPE. This broad phenotype profile is similar to HLA-A*31:01, which is associated with an increased risk of CBZ-induced SJS, hypersensitivity syndrome, and MPE in white[29] and Japanese populations.[28]

The meta-analysis demonstrated that HLA-A*24:02 is also a risk factor for aromatic AED–induced cADRs in populations other than southern Han Chinese. In contrast to HLA-B*15:02, which is specifically prevalent in some populations in southeast Asia, HLA-A*24:02 is prevalent in most of the populations (http://www.allelefrequencies.net). The association between HLA and CBZ-SJS/TEN is generally ethnically specific such as HLA-B*15:02 in populations in south China and southeast Asia, with sensitivities varying from 69.6% (the present study) to 100%,[12–17,20] and HLA-A*31:01 in white[29] and Japanese populations.[35] Notably, the specificity of HLA-B*15:02 for CBZ-SJS/TEN appears to correlate with phenotype severity.[36] In Taiwanese cases with CBZ-SJS/TEN with >5% skin detachment, the HLA-B*15:02 carrier rate was as high as 100%, whereas in more common cases with <5% skin detachment, this rate varied from 80.0% to 87.7%; HLA-A*31:01 was also demonstrated to be a risk factor for MPE in Taiwanese populations.[37] These data suggested that ethnic specificity is less significant for the milder phenotype.[38] In these relatively milder and common cases, an HLA risk factor typically accounts for a portion of the cases such as HLA-A*31:01 in 42% of CBZ-induced SJS cases in whites[29] and 60.7% of cases in Japanese.[28] Therefore, the role of other HLA risk factors such as HLA-A*24:02 should be evaluated further.

Our study had some limitations. First, it focused only on HLAs. In addition to HLAs, other genetic and host factors might play a role in aromatic AED–induced cADRs. A recent genome-wide association study of common variants from Taiwan showed that the CYP2C9*3 allele of the drug-metabolizing enzyme might be involved in PHT-induced SJS/TEN.[30] The role of rare variants remains to be investigated. Our previous study demonstrated that a history of allergy is a risk factor for oxcarbazepine-induced MPE.[39] Second, despite recruitment from 8 centers, there were few cases of PHT-induced SJS/TEN. Third, although the meta-analyses suggested that HLA-A*24:02 is a common risk factor for aromatic AED–induced cADRs in other ethnic populations, further studies in larger cohorts from these populations are needed to verify this association. Indeed, the potential roles of HLA-B*15:11, HLA-B*15:01, and HLA-A*02:01 in aromatic AED–induced SJS/TEN and the interactions between HLA-A and HLA-B require further verification.

In the present study, positivity for HLA-A*24:02 showed a sensitivity of 36.3% and a specificity of 84.7% for aromatic AED–induced SJS/TEN, which were similar to those for HLA-A*31:01 for CBZ-induced hypersensitivity syndrome observed in northern European populations (37.0% and 96.1%, respectively). The combination of HLA-A*24:02 and HLA-B*15:02 showed a sensitivity of 72.5% and a specificity of 69.0% for aromatic AED–induced SJS/TEN. SJS/TEN is a life-threatening disorder, and HLA-A*24:02 is prevalent; therefore, our findings suggested that

Figure 2 legend, continued:
Data were from 14 studies, including 7 that used drug-tolerant controls, 5 that used population controls, and 2 that used both types of controls, including populations from Japan, Korea, Malaysia, Mexico, Norway, and China (e-supplement). Data from tolerant controls (A) and population controls (B) were analyzed separately. The phenotypes of cADRs included SJS/TEN, MPE, and unspecified cADRs, according to the descriptions in the original reports. I^2 and τ^2 and represent measures of heterogeneity. Study weighting (indicated by different sizes of squares) refers to the proportion of participants who were recruited from each study. Horizontal lines represent 95% CIs; diamonds indicate pooled ORs. AED = antiepileptic drug; cADRs = cutaneous adverse drug reactions; CBZ = carbamazepine; CI = confidence interval; HLA = human leukocyte antigen; LTG = lamotrigine; MPE = maculopapular exanthema; OR = odds ratio; PHT = phenytoin; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

in southern China, screening for HLA-A*24:02 should be considered before aromatic AEDs are prescribed, in addition to screening for HLA-B*15:02 before CBZ is prescribed. In other populations, further studies in larger cohorts are needed before a similar recommendation can be made.

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AUTHOR CONTRIBUTIONS

W.P. Liao and P. Kwan conceptualized the study, analyzed and interpreted the data, and drafted and revised the manuscript. W.P. Liao and P. Kwan had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Y.-W. Shi and F.-L. Min analyzed and interpreted the data, drafted and revised the manuscript, and contributed to the statistical analysis. J. Wang and B.J. Mao contributed to the statistical analysis. All authors collected data, revised the manuscript, and contributed to the writing.

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