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Review

Association between HLA alleles and lamotrigine-induced cutaneous adverse drug reactions in Asian populations: A meta-analysis

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ABSTRACT

Purpose: The aim of this study was to assess the association between human leukocyte antigen (HLA) variants and lamotrigine (LTG)-induced cutaneous adverse drug reactions (cARDs).

Methods: A comprehensive literature search was conducted on the relationship of HLA alleles with LTG-induced cADRs in Asian populations, through PubMed, Embase, and Cochrane Library. The last search was in February 2018. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was used to access the strength of the association between an HLA allele and LTG-induced cADRs.

Results: A total of 11 studies met the inclusion criteria and were enrolled in our meta- analysis, which were based on Chinese, Korean, and Thai populations. Among these populations, we observed that HLA-B*1502 is a risk allele for LTG-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in Chinese populations (pooled OR 2.4, 95% CI: 1.20–4.78, P = 0.01), HLA-A*2402 was found to be a significant risk allele for both SJS/TEN (pooled OR 3.50, 95% CI: 1.61–7.59, P = 0.002) and maculopapular eruption (MPE) (pooled OR 2.14, 95% CI: 1.10–4.16, P = 0.03), and HLA-B*3303 was considered to be a protective marker for MPE in Chinese and Korean populations (pooled OR 0.2, 95% CI 0.06–0.64, P = 0.007).

Conclusions: In Asian populations, HLA-B*1502 is a risk factor for LTG-induced bullous lesions such as SJS/TEN in Chinese populations, and HLA-A*2402 is associated with the susceptibility to either SJS/TEN or MPE. HLA-A*3303 is a protective allele against LTG-induced MPE in Chinese and Korean populations.

1. Introduction

Aromatic antiepileptic drugs (AEDs), including carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), and phenytoin (PHT), are among the most common causes of cutaneous adverse drug reactions (cADRs) because of their similar structure. The mortality rate of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) can be as high as 10% and 40%, respectively [1], and aromatic AEDs are among the most common causes of severe cutaneous reactions [2]. cADRs are categorized into bullous and non-bullous skin lesions by pathogenesis [3]. Non-bullous skin lesions vary from mild maculopapular eruptions (MPE), with increasing severity, to hypersensitivity syndrome (HSS). SJS and TEN are bullous lesions. The mechanism underlying drug-induced SJS/TEN might differ from that of MPE/HSS, and researchers often discuss the association between SJS/TEN and MPE/HSS with the genes separately [3,4]. The hapten model and the pharmacological-interaction model provide possible explanations of the process [5]. The hapten model concept indicates covalent binding of a drug or chemical to proteins, modifying the latter and rendering this newly generated complex to the specific major histocompatibility complex (MHC) molecule. MHC class I subsequently presents the complex to the CD8 + T cell, which activates cytotoxic T lymphocytes and natural killer T cells, resulting in secretion of granulysin and other cytotoxic proteins/chemokines that lead to the eruption of SJS/TEN [6]. Different from SJS/TEN, aromatic AEDs are presented to CD4 + T cells by MHC class II expressed on the surface of antigen-presenting cells [3] CD4 + T cells secrete IL-5、perforin and granzymes, which play a significant role in the pathogenesis of MPE [7]. In pharmacological-interaction concept, although a labile binding of the drug to the MHC-peptide complex which is easily removed by simple washing was found, T cell receptor(TCR) can interact with the drug-MHC complex with a high affinity and are capable of generating receptor-mediated signals [5].

The variant allele HLA-B*1502 was found to be strongly associated with greater risk of SJS and TEN in patients treated with CBZ or OXC. The frequency of HLA alleles differs among races, and HLA-B*1502 is common in East Asians (6.9%) [8]; Thus the US Food and Drug Administration (FDA) recommends screening the allele in individuals of

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Asian ancestry before initiating treatment with CBZ [9]. In addition, it was found that an increasing number of genetic polymorphisms in HLA genes predict CBZ induced cADRs in Asian countries [10,11]. LTG and CBZ belong to the aromatic AEDs and each possesses an aromatic ring structure. Aromatic AEDs causing cADRs may have a similar pathogenesis while there is limited evidence of HLA alleles associated with LTG-induced cADRs due to small sample sizes which may contribute observed variatioins. Therefore, the aim of our meta-analysis is to systematically assess the association between HLA alleles with LTG-induced cADRs in the Asian populations.

2. Materials and methods

2.1. Data sources and literature searches

A comprehensive search of the literature in Embase, PubMed, and the Cochrane database of systematic reviews was carried out, from inception to February 24, 2018. The search terms used were “human leukocyte antigen” OR “HLA Antigens” OR “Antigens, HLA” OR “HLA” AND “lamotrigine” OR “LTG” AND “Stevens-Johnson Syndrome” OR “SJS” OR “toxic epidermal necrolysis” OR “TEN” OR “maculopapular eruption” OR “maculopapular rash” OR “MPE” OR “hypersensitivity syndrome” OR “HSS”. The language of studies was restricted to English. We further searched the references of the included articles to obtain other pertinent studies. Unpublished studies or articles without the full-text available were not taken into consideration.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included. (1) The article explored the association between HLA alleles and LTG-induced cADRs categorized into the specific types (SJS/TEN, MPE, HSS, or DRESS); (2) the study had a case–control or cohort study design; (3) the article compared patients with LTG-induced cADRs to LTG-tolerant patients or the general population; and (4) the article presented sufficient data to calculate the frequency of a variant HLA allele among groups. The exclusion criteria is as follows: (1) case reports or case series, review articles, basic genetic research, and duplicate studies were excluded, (2) research based on non-Asian populations were excluded because the frequency of HLA alleles is of huge difference in Asian populations, Caucasians, and African populations, (3) patients are taking other drugs that can cause cADRs, such as CBZ, OXC, and PHT (Fig. 1).

2.3. Data extraction and quality assessment

Two reviewers (YD, SL) independently extracted data, and discrepancies were resolved through group discussions or by seeking the consensus of a third reviewer. The date extracted included the following information: first author, publication year, race/ethnicity, study design, types of cADRs, data on detection of HLA variants in each patient and control, and HLA genotyping method. The HLA variants data were extracted for which the frequency data were available in at least two studies. Finally, a meta-analysis was performed to evaluate the association between five HLA variants among patients showing cADRs and controls showing cADRs. The HLA variants included two spanning HLA-A loci (2402, 3303) and three spanning HLA-B loci (1502, 4001, 5801).

According to the clinical outcome presented in the selected articles, bullous and non-bullous cADRs were analyzed separately because their pathomechanism was different. SJS and TEN were analyzed together because they were thought to be variants of the bullous cADRs. MPE and HSS belong to the non-bullous cADRs. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included articles based on the following three aspects: selection, comparability, and exposure or outcome [12].

2.4. Statistical analysis

All the analyses were carried out using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). The overall odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to identify the association between the presence of HLA variant in at least one allele and several types of LTG-induced cADRs. The frequency data were converted to the number of carrier patients with special variant HLA loci present in at least one allele. Forest plots were used to visualize meta-analysis results. Heterogeneity was tested by chi square–based Cochran’s Q-statistics and I^2 metric statistics. If no heterogeneity was presented, fixed-effects models were used to analyze the data. The significance of pooled ORs was calculated using the Z value. Sensitivity analysis was carried out by removing one study at a time and weighing the impact of excluded studies by calculating the pooled ORs of those left. Due to the insufficient number of studies, the funnel plots could hardly assess publication bias, so we used the fail-safe number with significance set at 0.05 (Nfs 0.05) for each meta-analysis.

3. Results

A total of 174 records were identified after searching the database, and the literature selection process is presented in Fig. 1. 11 articles that met the inclusion criteria were included. The characteristics of the studies included are shown in Table 1. All are case-control studies based on Asian populations, and comprise of 73 LTG-induced SJS/TEN patients, 144 LTG-induced MPE patients and 426 LTG-tolerant patients. The diagnostic criteria of SJS/TEN is based on clinical morphology defined by Roujeau and Stern [1], and MPE is the lesion characterized by cutaneous fine pink macules which usually fade within 1–2 weeks following cessation of drug treatment [3]. We used NOS to assess the quality of the studies, with a limit of > 5.

3.1. Association between HLA-B*1502 and lamotrigine-induced cADRs

A total of 54 LTG-induced SJS/TEN cases and 313 controls were included in the 7 studies. Six studies that examined HLA-B*1502 with LTG-induced MPE were selected. The standard forest plot is shown in Fig. 2. No obvious heterogeneity existed ($I^2 = 0$ and $P = 0.8$, $I^2 = 39\%$ and $P = 0.14$). The fixed-effects model was selected to calculate the pooled ORs and 95% CIs. HLA-B*1502 was detected in 15 of 54 LTG-induced SJS/TEN cases, and 41 of 313 controls, We detected a significant association of HLA-B*1502 with LTG-induced SJS/TEN (pooled OR 2.4, 95% CI: 1.20–4.78, $P = 0.01$). Among the LTG-induced MPE studies, there were 165 cases and 274 tolerant controls. 19 of 165 were carriers of the allele and 35 were carriers out of 274 LTG-tolerant controls. In total, there was no significant association between the patients carrying HLA-B*1502 and the process of LTG-induced MPE (OR: 1.07, 95% CI: 0.59–1.95, $P = 0.82$). HLA-B*1502 was found to be a risk allele for LTG-induced SJS/TEN but when tested was not significantly associated with LTG-induced MPE.

3.2. Association between HLA-A*2402 and lamotrigine-induced cADRs

For HLA-A*2402, 40 cases and 131 LTG-tolerant controls of 2 studies were selected for meta-analysis of LTG-induced SJS/TEN, and 28 cases and 28 LTG-tolerant controls for LTG-induced MPE. Fig. 3 shows the pooled ORs. Fig. 3 shows the pooled ORs. No significant heterogeneity existed ($I^2 = 0$ and $P = 0.49$, $I^2 = 4\%$ and $P = 0.31$), and we used the fixed-effects model to analyze the data. The carrier frequency of the cases (21/40) in LTG-SJS/TEN was greater than in the LTG-tolerant controls (27/131). For LTG-MPE cases, the carrier frequency was 28/76, whereas it was 28/131 in controls. Overall, HLA-A*2402 was found to be a significant risk allele for both SJS/TEN (pooled OR: 3.50, 95% CI: 1.61–7.59, $P = 0.002$) and MPE (pooled OR 2.14, 95% CI: 1.10–4.16, $P = 0.03$).

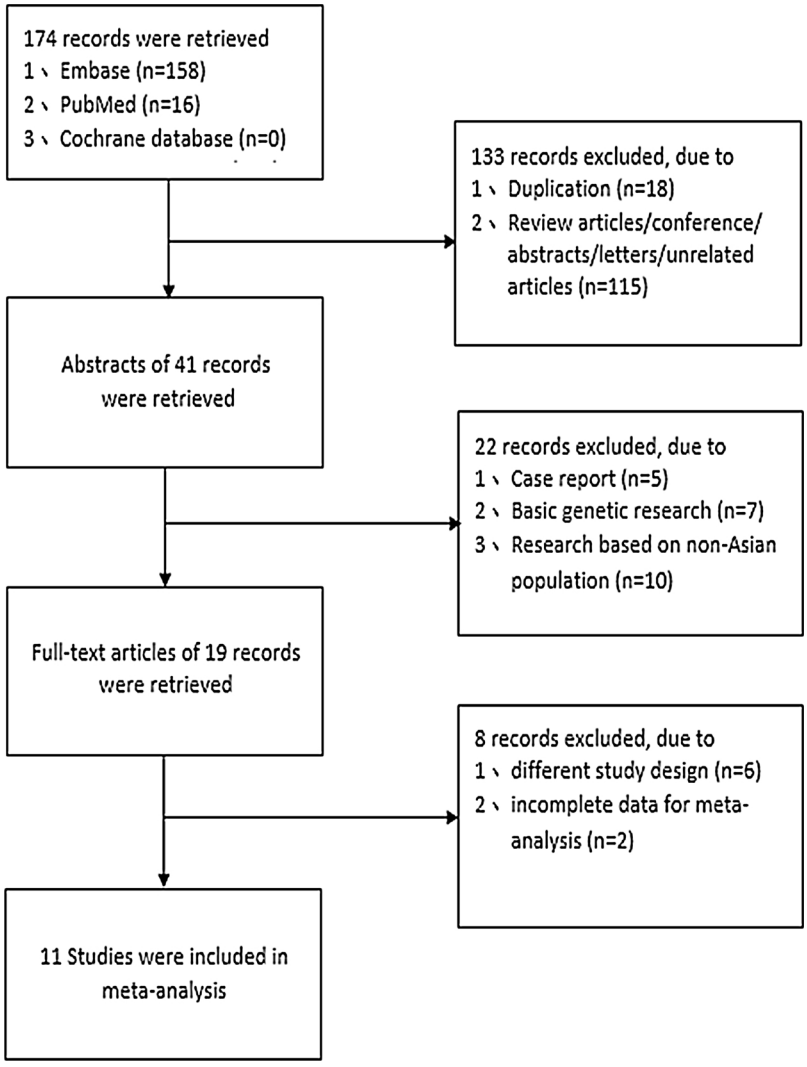

Fig. 1. Flow diagram for study identification, screening exclusion, and inclusion.

3.3. Association between HLA-B*3303 and lamotrigine-induced MPE

The data of 3 studies were selected to be extracted for analysis of the association between HLA-B*3303 and LTG-induced MPE; heterogeneity was found to arise (P = 0.0007, I = 86%). No heterogeneity was detected by exclusion of the Thai population, using the fixed-effects model (I^2: 0%, P = 0.75). The forest plot is shown in Fig. 4. 64 patients in LTG-induced MPE cases and 73 controls carried the allele, so there was a trend of higher carrier rate of HLA-B*3303 in LTG-tolerant controls. The pooled OR was 0.2 (95% CI: 0.06–0.64, P = 0.007), which indicated that HLA-B*3303 was a protective allele.

3.4. Association between HLA-B*5801 and lamotrigine-induced MPE

75 cases and 101 LTG-tolerant cases were extracted from 3 studies. The relationship between HLA-B*5801 and LTG-induced MPE is shown in Fig. 5. Heterogeneity was minimal (I2 = 0) and was not significant (P = 0.75), and the fixed-effects model was used. The carrier rate of HLA-B*5801 was 8/75 and the tolerant controls were 11/101. The allele does not implicate a significant correlation with LTG-MPE (OR 1.03, 95% CI: 0.39–2.72, P = 0.95).

3.5. Sensitivity analysis

To examine the robustness of the results, we carried out the sensitivity analysis by removing one study or studies belonging to a specific ethnicity each time and cal-culating the pooled ORs of the remaining studies. The fixed-effects models were used to pool the data (Table 3). We observed that the exclusion of Chinese subgroups led to loss of significance when pooled with the remaining studies investigating the association between HLA-B*1502 and LTG-induced SJS/TEN (OR 2.90, 95% CI: 0.63–13.45, P = 0.17). It indicated that HLA-B*1502 was a stronger risk factor among Chinese populations than among other Asian ethnicities for suscepti-bility to SJS/TEN. None of the individual studies influenced the pooled ORs when studying the susceptibility of HLA-B*5801, indicating that the result was robu-st. For HLA-A*3303, exclusion of the Thai population led to loss of heterogeneity (I^2: 0%), indicating such heterogeneity probably arose from ethnic difference in various location of the Northern Hemisphere; and it was indicated the frequency of HLA-A*3303 in Korean and Chinese populations is similar (http://www.allelefrequencies.net/), As a result, HLA-A*3303 was thought to be a protective allele in Korean and Chinese populations.

3.6. Publication bias

Nfs0.05 was used to explore the publication bias for the insufficient number of included studies; the results shown in Table 2 suggest that the associations were reliable.

Table 1
Characteristics of studies included in the meta-analysis.

References	Population	Phenotypes studied	Case/control	Patients on LTG (n)	cADRs patients					Drug tolerant patients	Normal controls	Method of geno-typing	Reported HLA alleles included in meta- analysis		Compar-Able group	NOS
					SJS/TEN(%)	MPE (%)	HSS (%)	Other (%)	Total (%)				HLA-A	HLA-B		
An et al. [13] (2010)	Han Chinese	SJS/TEN and MPE	Case: Patients who developed cADRs within 8 weeks after treatment with LTG without any other obvious cause of the disease. Control: Patients who were treated with LTG for > 3 months did not suffer from any cutaneous manifestations.	46	3(6.5)	22(47.8)	0	0	25(54.3)	21	71	PCR-SBT	N	1502	Nontolerant vs. tolerant Nontolerant vs. normal controls	7
Hung et al. [14] (2010)	Han Chinese	SJS/TEN	Case: Patients who developed SJS/TEN within 2 months after receiving an AED and the symptoms resolved upon withdrawal of the drug. Control: Patients who had been on an AED for more than 3 months did not show any cADRs.	67	6(8.6)	0	0	0	6(8.6)	67	N	PCR-SSOP/ PCR-SBT	N	1502	Nontolerant vs. tolerant	5
Shi et al. [26] (2011)	Han Chinese	SJS and MPE	Case: Patients developed cADRs within 8 weeks after commencing LTG and for which no other causes were found. Control: Patients who had been on an AED for more than 3 months did not show any cADRs.	43	2(4.6)	12(27.9)	0	0	14(55.8)	29	264	PCR-SSP/ PCR-SBT	N	1502, 5801	Nontolerant 7 vs. tolerant Nontolerant vs. normal controls	7
Cheung et al. [27] (2013)	Han Chinese	SJS/TEN	Case: Patients who developed SJS/TEN within 12 weeks after commencing an AED and for which no other causes were found were eligible for inclusion as cases. Control: Patients who had taken an AED for at least 3 months without developing cADRs.	36	6(16.7)	0	0	0	6(16.7)	30	N	PCR-SBT	N	5801, 1502	Nontolerant vs. tolerant	6
Li et al. [18] (2013)	Han Chinese	MPE	Case: Patients who showed cADRs on CBZ or LTG treatment. Control: Patients who did not suffer from cADRs on CBZ or LTG treatment.	85	0	43(50.6)	0	0	43(50.6)	42	77	PCR-SBT	3303	1502, 5801	Nontolerant vs. tolerant, Nontolerant vs. normal controls	6
Kwan et al. [22] (2014)	Hong Kong Chinese	SJS/TEN	Case: Patients who presented with SJS/ TEN within 12 weeks after commencing an AED. Control: Patients who took an AED for at least 3 months without developing skin rash.	36	6(16.7)	0	0	0	6(16.7)	30	N	PCR-SBT	N	5801, 1502	Nontolerant vs. tolerant	6
Wang et al. [28] (2014)	Han Chinese	SJS/TEN	Case: Patients who developed AED-induced SJS/TEN after taking AEDs for less than 8 weeks. Control: Patients who had been on an AED for more than 3 months without experiencing an allergic reaction.	20	7(35)	0	0	0	7(35)	13	N	PCR-SBT	3303	1502	Nontolerant vs. tolerant	6

(*continued on next page*)

Table 1 (*continued*)

References	Population	Phenotypes studied	Case/control	Patients on LTG (n)	cADRs patients					Drug tolerant patients	Normal controls	Method of geno-typing	Reported HLA alleles included in meta- analysis		Compar-Able group	NOS
					SJS/TEN(%)	MPE (%)	HSS (%)	Other (%)	Total (%)				HLA-A	HLA-B		
Moon et al. [20] (2015)	Korean	MPE	Case: Patients developed MPE within 6 weeks after the last dose escalation of LTG or when LTG was the only offending drug administered to the patient, and the rash was resolved after discontinuation of LTG. Control: Patients who had received ≥300 mg/day of LTG and had a documented medical history of LTG serum levels > 10 lg/ml without any cADRs during a minimum of 1 year of LTG treatment.	50	0	21(42)	0	0	21(42)	29	485	PCR-SBT	2402	3303, 5801, 1502	Nontolerant vs. tolerant, Nontolerant vs. normal controls	5
Kim et al. [21] (2017)	Korean	SCAR	Case: Patients who showed SCAR on LTG treatment. Control: Patients who did not suffer from cADRs on LTG treatment.	47	18(38.3)	0	0	0	18(38.3)	58	970	PCR-SSOP	2402	N	Nontolerant vs. tolerant, Nontolerant vs. normal controls	5
Koomdee et al. [15] (2017)	Thai	SJS and MPE	Case: Patients who developed cADRs within 2 months after initiating LTG treatment. Control: Patients who had been taking LTG for more than 6 months without evidence of cADRs.	65	4(6.2)	10(15.4)	0	1(1.5)	15(23.1)	50	1355	PCR-SSOs	N	1502, 3303	Nontolerant vs. tolerant, Nontolerant vs. normal controls	7
Shi et al. [19] (2017)	Han Chinese	SJS and MPE	Case: Patients who developed cADRs within 8 weeks of beginning an aromatic AED for which no other causes were found. Control: Patients who took aromatic AEDs for at least 3 months without evidence of cADRs.	124	22(17.7)	59(47.6)	0	0	81(65.3)	102	N	PCR-SBT	2402	1502	Nontolerant vs. tolerant	5

LTG, lamotrigine.
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular eruption.
NOS, Newcastle-Ottawa Scale.

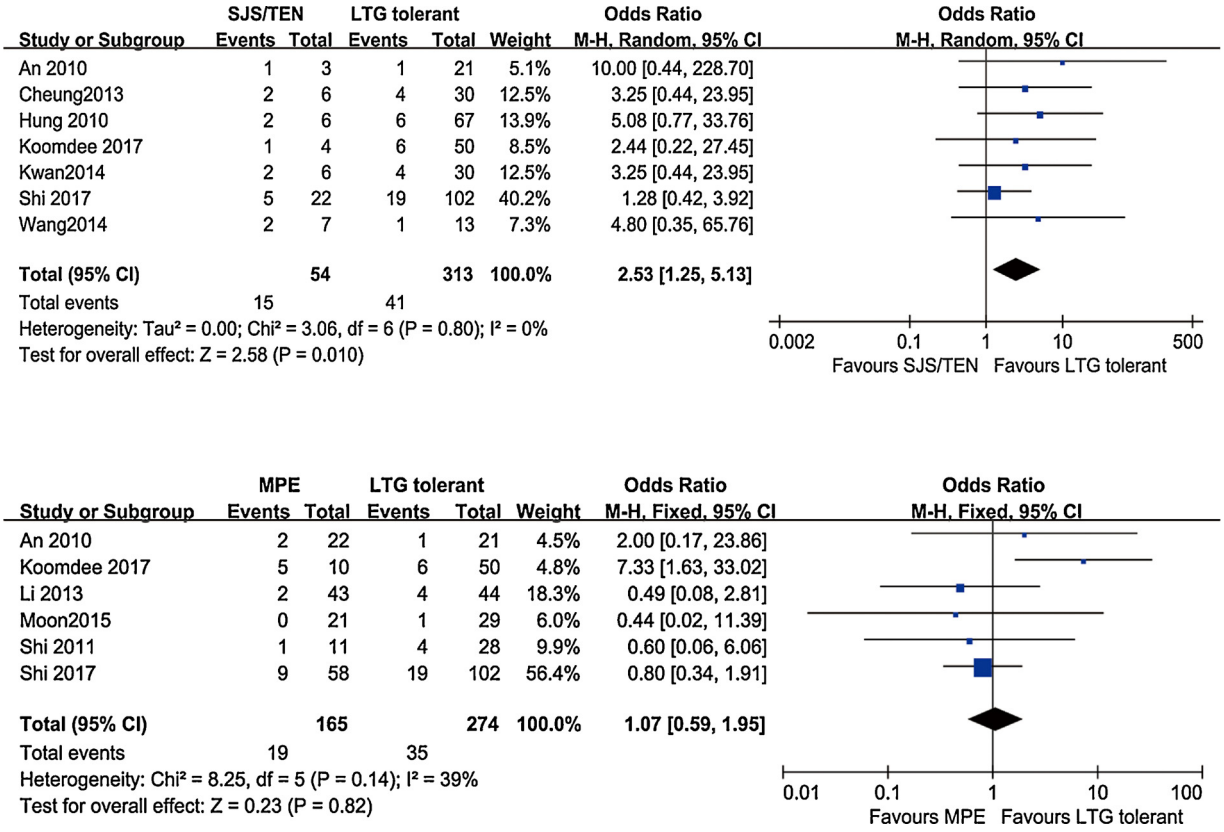

Fig. 2. Pooled analysis of LTG-induced SJS/TEN, MPE among carriers of the HLA-B*1502 allele.

4. Discussion

In our meta-analysis, we found HLA-B*1502 correlates with LTG-induced SJS/TEN in the Chinese populations. HLA-A*2402 is associated with the susceptibility to both SJS/TEN and MPE. HLA-A*3303 is a protective allele in the Chinese and Korean populations. Contrary to previous findings, there is no significant difference in the frequency of subjects with the HLA-B*1502 allele between both SJS/TEN and controls [13,14]. HLA-B*1502 is a risk factor for LTG-induced bullous lesions including SJS or TEN, but it is not statistically associated with non-bullous lesions such as MPE. The odds ratio for LTG-induced SJS/TEN in HLA-B*1502 carriers is 2.4 times that in LTG-tolerant controls. Contrary to the observation indicating HLA-B*3303 is a risk allele for MPE in Thai populations [15], our review suggests that it is a protective

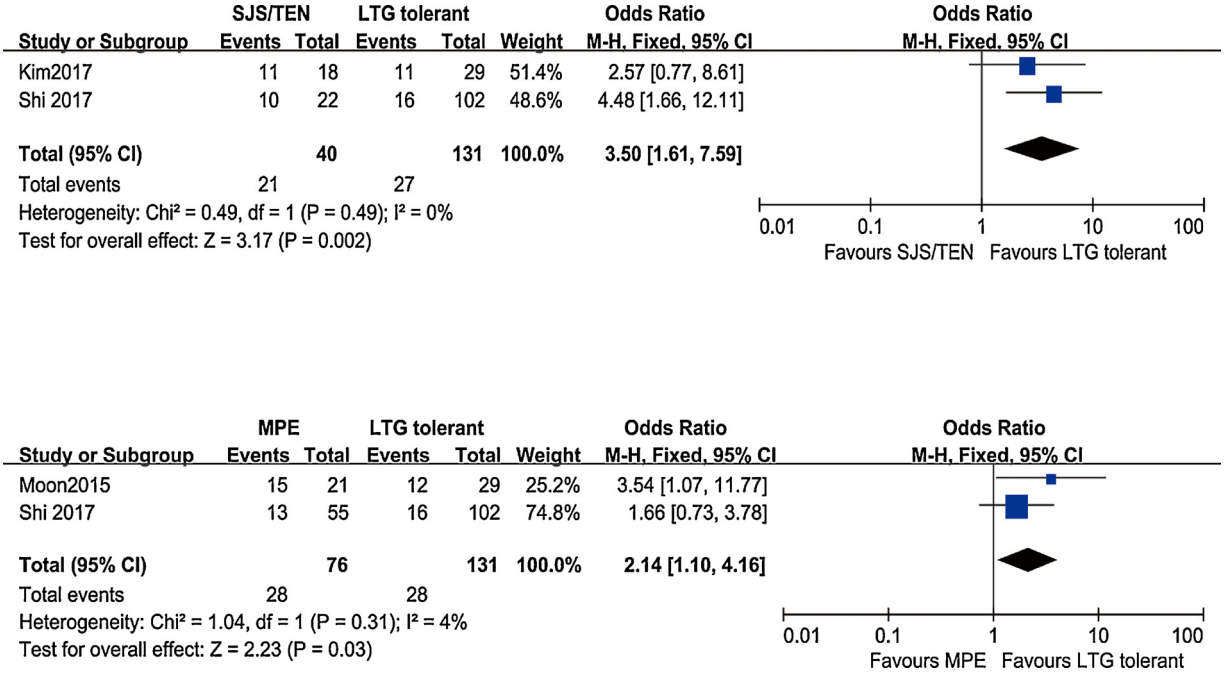

Fig. 3. Pooled analysis of LTG-induced SJS/TEN, MPE among carriers of the HLA-B*2402 allele.

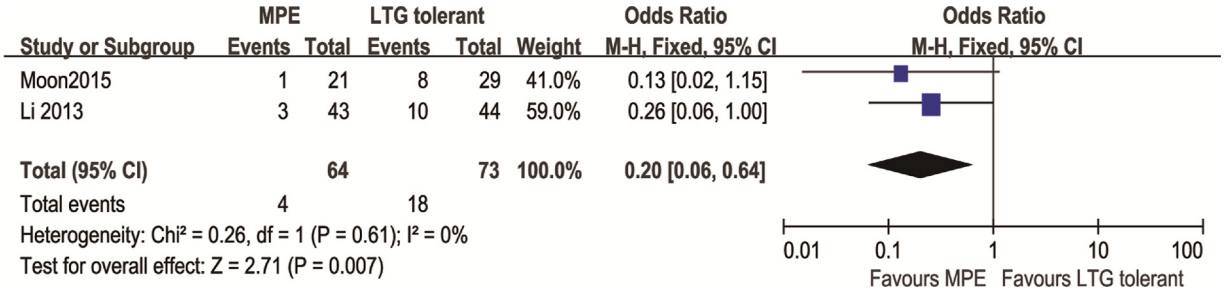

Fig. 4. Pooled analysis of LTG-Induced MPE among carriers of the HLA-B*3303 allele.

factor for MPE because of the low frequency of expression in Chinese and Korean patients. HLA-B*5801 was found to have a strong association with allopurinol-induced HSS and SJS/TEN in the Chinese and European populations [16,17]. Li revealed that HLA-B*5801 might be a protective allele against CBZ-induced MPE [18]. In our meta-analysis, there is no statistical significance between HLA-B*5801 and LTG-MPE. For HLA-A*2402, Shi et al. demonstrated that the allele is a major risk factor in LTG-induced SJS/TEN but does not have significant associations with MPE [19]. Moon indicated that higher frequencies of HLA-A*2402 increases susceptibility to MPE [20]. Kim found that the allele is not statistically significant in association with SJS/TEN [21]. Our meta-analysis confirmed an increased susceptibility to both bullous and non-bullous cADRs in Chinese and Korean populations carrying HLA-A*2402. The OR for SJS or TEN cases in HLA-A*2402 carriers is 3.50 times that of tolerant controls. For MPE or HSS cases, it is 2.14 times that of matched controls. A lower carrier rate of HLA-B*4001 was noted in CBZ-induced cADRs cases in the present study, compared with CBZ-tolerant controls. Kwan found there is no significant correlation between HLA-B*4001 and LTG-induced SJS/TEN [22]. Due to the lack of data, the analysis of HLA-B*4001 cannot be carried out, and further investigation is needed.

The finding in this updated meta-analysis for the correlation between HLA-B*1502 and LTG-induced SJS/TEN is statistically significant. However, we observed that HLA-B*1502 has no significant association with LTG-induced MPE, which might accord with the different immunopathogenesis of those reactions. MPE is caused by skin-infiltrating CD4 + T cells, which secrete IL-5, perforin, and granzymes, whereas SJS/TEN belong to the bullous reactions caused by cytotoxic CD8 + T cells [6,7]. The HLA-B allele can elicit immune responses by presenting endogenous antigens to the drug. The metabolites in turn bond with peptides which are then presented by the HLA-B allele and recognized by CD8 + T cells [6]. MHC class II genes were reported to be involved in the pathogenesis of MPE/HSS. However, HLA-A*3101 allele belonging to MHC class I genes was considered to be correlated with MPE, which disagrees with the observation that MHC class II genes were involved in the process [23]. One possible explanation is that genes associated with MPE lied in the vicinity of the HLA-A loci, which is in linkage disequilibrium with HLA-A*3101 [3]. HLA-A*2402 belonging to MHC class I genes in the meta-analysis is also found to be associated with LTG-induced MPE, indicating the pathogenesis remains unclear. In recent years, in silico analysis was applied and indicated the details of the molecular behavior of HLA-B alleles in the pathogenesis of SJS/TEN; the evidence of significant association was found between CBZ-induced SJS and HLA-B75 molecules [24]. Moreover, the specific HLA class II haplotypes were found to be protective alleles against systemic disease by regulating cytokine responses [25]. The mechanism of HLA class I or II as protective allele against cADRs is not fully understood, requiring further exploration in the future.

This meta-analysis had several limitations. First, the sample size of most studies was small, and this might reduce the statistical power to detect associations. Second, our data were extracted from published studies, and preexisting publication bias would affect our results. Last, more studies are needed with different ethnicities in Asian populations in the future.

5. Conclusion

The meta-analysis revealed that HLA-B*1502 is a risk allele for LTG-induced SJS/TEN in Chinese populations. HLA-A*2402 is statistically associated with the susceptibility to either SJS/TEN or MPE. HLA-A*3303 was considered a protective allele against LTG-induced MPE in Korean and Chinese populations. Large-size samples in future studies are needed to validate our findings further and confirm the involvement of associated HLA alleles with LTG-induced cADRs in Asian populations.

Conflict of interest

The authors have no actual or potential conflicts of interest related to this manuscript.

Ethical standards

The current meta-analysis does not report original data from human or animal subjects. Please consult the original publications for information about ethical procedures.

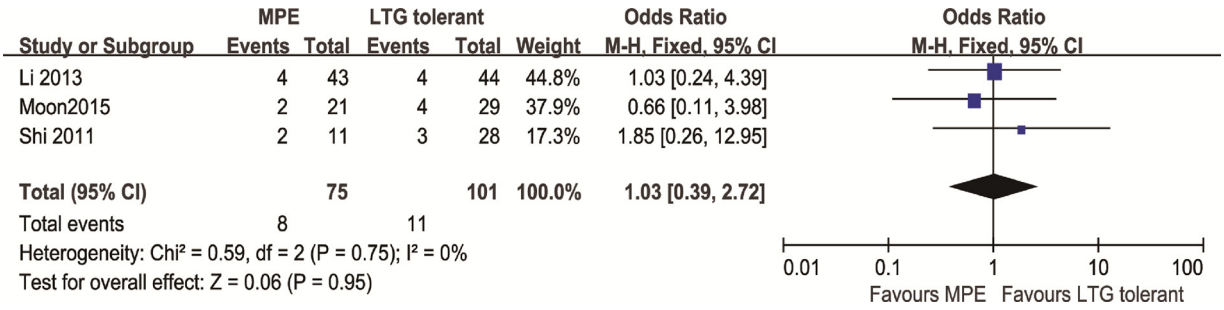

Fig. 5. Pooled analysis of LTG-induced MPE among carriers of the HLA-B*5801 allele.

Table 2
Pooled odds ratios for studies.

HLA types	Number of studies(n)	Population	Patients on LTG(n)	cADRs	Patients showing cADRs with LTG[n(%)]		LTG-tolerant patients[n(%)]		OR (95% CI)	p	I^2%	Model	Fail-safe number
					HLA positive	total	HLA positive	total					
HLA-A *2402	2	Chinese (Shi) Korean (Kim)	171	SJS/TEN	21(12.3)	40(23.4)	27(15.8)	131(76.6)	3.50 [1.61, 7.59]	**0.002**	0	F	6.07044
HLA-B *1502	7	Chinese (An) Chinese (Cheung) Chinese (Hung) Chinese (Kwan) Chinese (Shi) Chinese (Wang) Thai (Koomdee)	367	SJS/TEN	15(4.1)	54(14.7)	41(11.2)	313(85.3)	2.40 [1.20, 4.78]	**0.01**	0	F	18.85961
HLA-A *2402	2	Chinese (Shi) Korean (Moon)	207	MPE	28(13.5)	76(36.7)	28(13.5)	131(63.3)	2.14 [1.10, 4.16]	**0.03**	4	F	2.11988
HLA-B *1502	6	Chinese (An) Chinese (Li) Chinese (Shi 2011) Chinese (Shi 2017) Korean (Moon) Thai (Koomdee)	439	MPE	19(4.3)	165(37.6)	35(8.0)	274(62.4)	1.07 [0.59, 1.95]	0.82	39	F	7.39851
HLA-B *3303	2	Chinese (Li) Korean (Moon)	137	MPE	4(2.9)	64(46.7)	18(13.1)	73(53.3)	0.20 [0.06, 0.64]	**0.007**	0	F	4.35305
HLA-B *5801	3	Chinese (Li) Chinese (Shi 2011) Korean (Moon)	176	MPE	8(4.5)	75(42.6)	11(6.25)	101(57.4)	1.03 [0.39, 2.72]	0.95	0	F	−2.53333

Bold characters highlight significantly associated alleles with respective P values.
LTG, lamotrigine; cADRs, cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular eruption; OR, odds ratio; CI, confidence interval.

Table 3
Sensitivity analysis with pooled odds ratios by removing one study or studies belonging to specific ethnicity each time.

HLA type	cADRs	Number of studies	population (references)	OR (95% CI)	P	I^2(%)
B*1502	SJS/TEN	6	All except Hong Kong Han Chinese (Kwan)	2.30[1.10,4.81]	**0.03**	0
	SJS/TEN	6	All except Thai (Koomdee)	2.39[1.16,4.92]	**0.02**	0
	SJS/TEN	2	All except Han Chinese (An, Cheung, Hung, Shi, Wang)	2.90[0.63,13.45]	0.17	0
	MPE	5	All except Korean (Moon)	1.11[0.61, 2.05]	0.73	49
	MPE	5	All except Thai (Koomdee)	0.75[0.38,1.49]	0.42	0
	MPE	2	All except Han Chinese (An, Li, Shi)	3.52[0.98,12.58]	0.05	60
A*3303	MPE	2	All except Han Chinese (Li)	1.33[0.52, 3.37]	0.55	90
		2	All except Korean (Moon)	1.11[0.48, 2.57]	0.80	91
		2	All except Thai (Koomdee)	0.20[0.06, 0.64]	**0.007**	0
B*5801	MPE	2	All except Korean (Moon)	1.26[0.39, 4.04]	0.70	0

Bold characters highlight significantly associated alleles with respective P values.
LTG, lamotrigine; cADRs, cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular eruption. OR, odds ratio; CI, confidence interval.

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References

[1] Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.
[2] Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600–7.
[3] Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006;16:297–306.
[4] Moon J, Kim TJ, Lim JA, Sunwoo JS, Byun JI, Lee ST, et al. HLA-B∗40:02 and HLA-DRB1∗04:03 as genetic markers for oxcarbazepine induced maculopapular eruption. Annals of Neurology 2016;80:S41.
[5] Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. Curr Opin Allergy Clin Immunol 2002;2:301–5.
[6] Ko TM, Chung WH, Wei CY, Shih HY, Chen JK, Lin CH, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol 2011;128:1266–76.
[7] Naisbitt DJ, Britschgi M, Wong G, Farrell J, Depta JP, Chadwick DW, et al. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. Mol Pharmacol 2003;63:732–41.
[8] Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine. update. Clin Pharmacol Ther 2017;103(2018):574–81.
[9] Food and Drug Administration Alert, Information for healthcare professionals: dangerous or even fatal skin reactions: carbamazepine. (Marketed as carbatrol, equetro, tegretol, and generics). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm, 2013, [Accessed 13.10].
[10] Sun D, Yu CH, Liu ZS, He XL, Hu JS, Wu GF, et al. Association of HLA-B*1502 and *1511 allele with antiepileptic drug-induced Stevens-Johnson syndrome in central China. J Huazhong Univ Sci Technolog Med Sci 2014;34:146–50.
[11] Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Human Molecular Genetics 2011;20:1034–41.
[12] Wells GA, Shea B, O'Connell D, Welch Peterson V, Losos M, Tugwell P, et al. The Newcastle-Ottawa Scale(NOS) for assessing the quality of nonrandomised studies in meta-analyses. Appl Eng Agric 2000;18:727–34.
[13] An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. Epilepsy Res 2010;92:226–30.
[14] Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RC, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349–56.
[15] Koomdee N, Pratoomwun J, Jantararoungtong T, Theeramoke V, Tassaneeyakul W, Klaewsongkram J, et al. Association of HLA-A and HLA-B alleles with Lamotrigine-Induced cutaneous adverse drug reactions in the Thai population. Front Pharmacol 2017;8:879.
[16] Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18:99–107.
[17] Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA 2005;102:4134–9.
[18] Li LJ, Hu FY, Wu XT, An DM, Yan B, Zhou D, et al. Predictive markers for carbamazepine and lamotrigine induced maculopapular exanthema in Han Chinese. Epilepsy Res 2013;106:296–300.
[19] Shi YW, Min FL, Zhou D, Qin B, Wang J, Hu FY, et al. HLA-A*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions. Neurology 2017;88:2183–91.
[20] Moon J, Park HK, Chu K, Sunwoo JS, Byun J, Lim JA, et al. The HLA-A*2402/Cw*0102 haplotype is associated with lamotrigine-induced maculopapular eruption in the Korean population. Epilepsia 2015;56:e161–7.
[21] Kim BK, Jung JW, Kim TB, Chang YS, Park HS, Moon J. HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population. Ann Allergy Asthma Immunol 2017;118:629–30.
[22] Kwan PK, Ng MH, Lo SV. Association between HLA-B*15:02 allele and antiepileptic drug-induced severe cutaneous reactions in Hong Kong Chinese: a population-based study. Hong Kong Med J 20, 2014, Suppl 7: 168.
[23] Moon J, Kim TJ, Lim JA, Sunwoo JS, Byun JI, Lee ST, et al. HLA-B*40:02 and DRB1*04:03 are risk factors for oxcarbazepine-induced maculopapular eruption. Epilepsia 2016;57:1879–86.
[24] Jaruthamsophon K, Tipmanee V, Sangiemchoey A, Sukasem C, Limprasert P. HLA-B*15:21 and carbamazepine-induced Stevens-Johnson syndrome: pooled-data and in silico analysis. Sci Rep 2017;7:45553.
[25] Kotb M, Norrby-Teglund A, McGeer A, El-Sherbini H, Dorak MT, Khurshid A, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat Med 2002;8:1398–404.
[26] Shi YW, Min FL, Liu XR, Zan LX, Gao MM, Yu MJ, et al. Hla-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population. Basic Clin Pharmacol Toxicol 2011;109:42–6.
[27] Cheung YK, Cheng SH, Chan EJ, Lo SV, Ng MH, Kwan P, et al. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia 2013;54:1307–14.
[28] Wang W, Hu FY, Wu XT, An DM, Yan B, Zhou D. Genetic predictors of Stevens-Johnson syndrome and toxic epidermal necrolysis induced by aromatic antiepileptic drugs among the Chinese Han population. Epilepsy Behav 2014;37:16–9.