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Association of *HLA-B*1502* allele with lamotrigine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: a meta-analysis

Tao Zeng[1,2], MD, Yue-Sheng Long[1], PhD, Fu-Li Min[1], MD, Wei-Ping Liao[1], MD, PhD, and Yi-Wu Shi[1], PhD

[1]Institute of Neuroscience and the Second Affiliated Hospital of Guangzhou Medical University, Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Guangzhou, China, and [2]Department of Neurology, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou, China

Correspondence
Yi-Wu Shi, PhD
Institute of Neuroscience, Second Affiliated Hospital of Guangzhou Medical University
Guangzhou, Guangdong 510260
China
E-mails: stoneyiwu@163.com, stoneyiwu@sohu.com

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Abstract

Background Despite several studies investigating the association between the human leukocyte antigen *HLA-B*1502* allele and lamotrigine-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Han Chinese subjects, the relationship remains unclear.

Objectives We performed a systematic review and meta-analysis to ascertain the association between the *HLA-B*1502* allele and lamotrigine-induced SJS and TEN in Han Chinese populations.

Methods We searched the biomedical literature archived in the MEDLINE, Cochrane Library, EMBASE, Chinese Biomedical, Chinese National Knowledge Infrastructure, and China Science and Technology Journal databases. Only studies investigating the association between *HLA-B*1502* and lamotrigine-induced SJS/TEN were included. We then performed a meta-analysis of the data in these studies.

Results Four studies including a total of 12 patients with SJS/TEN and 128 lamotrigine-tolerant control subjects were identified. The *HLA-B*1502* allele was present in 33.3% (four of 12) of lamotrigine-induced SJS/TEN cases but in only 9.4% (12 of 128) of lamotrigine-tolerant controls. The occurrence of SJS/TEN was thus associated with the presence of the *HLA-B*1502* allele (odds ratio: 4.98, 95% confidence interval 1.43–17.28; $P < 0.05$).

Conclusions We found a statistical association between *HLA-B*1502* and lamotrigine-induced SJS/TEN in Han Chinese subjects. Future studies with larger sample sizes are suggested to verify the results.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening severe adverse cutaneous reactions. These conditions occur at incidences of one to seven cases and 0.4 to 1.5 cases, respectively, per million population but are associated with mortality rates of 1–5% in the case of SJS and up to 25–35% in TEN.[1–6] Clinical manifestations of SJS and TEN are characterized by erythematous and erosive lesions of the skin, conjunctiva, and mucous membranes, as well as systemic symptoms.[3]

Recent studies indicate that aromatic antiepileptic drugs (AEDs), including carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG), are the major causative agents of SJS/TEN. The mortality associated with AED-induced SJS/TEN is 6.1%.[7]

Pharmacogenomic studies have shown that human leukocyte antigen (HLA) alleles are associated with AED-induced SJS/TEN and that genetic susceptibility to CBZ-induced cutaneous adverse drug reactions is ethnicity-specific.[8] Because LTG and CBZ are similar in structure, several studies on the relationship between HLA-B and LTG-associated SJS/TEN have been carried out in people of Han Chinese and White European ethnicity, respectively. To date, no association has emerged between *HLA-B*1502* and LTG-induced SJS/TEN in White Europeans,[9] and the association in Han Chinese is uncertain owing to the small sample sizes used in the various studies.[10–13] Because the combined incidence of SJS/TEN is higher in Han Chinese subjects[8] and the frequency of HLA alleles is racially diverse, we conducted a systemic review and quantitative analysis of the relationship

between the *HLA-B*1502* allele and LTG-induced SJS/TEN in Han Chinese populations.

Materials and methods

Information sources and search strategy

We performed a complete search of material archived in the electronic databases of the Cochrane Library, MEDLINE, EMBASE, the Chinese Biomedical Database (CBM), the Chinese National Knowledge Infrastructure (CNKI), and the China Science and Technology Journal (CSJT). The search terms were: "HLA-B" OR "human leukocyte antigen" AND "lamotrigine" OR "Lamictal" AND "Stevens–Johnson syndrome" OR "toxic epidermal necrolysis" OR "severe cutaneous reaction". Corresponding Chinese terms were also used. The last search was conducted on September 24, 2012.

Study selection

The following criteria were used for the selection of studies: (i) studies must have investigated the association between the *HLA-B*1502* allele and LTG-induced SJS/TEN; (ii) studies must have used a case–control or cohort design and must have obtained the frequencies of the *HLA-B*1502* in the case and control groups; and (iii) studies must describe SJS/TEN patients according to the extent of body surface area (BSA) affected as SJS (<10% of BSA), SJS/TEN overlap (10–30% of BSA), and TEN (>30% of BSA).[14] Animal studies, case reports, studies in non-Han Chinese subjects, and repeat studies were excluded.

Data extraction and quality assessment

According to the study selection criteria, all data were extracted independently by two reviewers. Disagreements were resolved by group discussion or by seeking the consensus of a third reviewer. Cohen's kappa (κ) coefficient was used as a measure of agreement between reviewers. Kappa values of 0.40–0.59 have been considered to reflect fair agreement, κ-values of 0.60–0.74 to reflect good agreement, and κ-values of $\geq$0.75 to reflect excellent agreement.[15] The data noted included the first author of the study, publication year, study type, the number of subjects positive for the *HLA-B*1502* allele among LTG-induced SJS/TEN patients and LTG-tolerant patients, total number of LTG-induced SJS/TEN patients and LTG-tolerant patients, patient demographics, and main results. The Newcastle–Ottawa Scale (NOS)[16] was used to assess the quality of the included literature.

Statistical analysis

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to identify the association between the *HLA-B*1502* allele and LTG-induced SJS/TEN. RevMan Version 5.0.24 (Cochrane Collaboration, Oxford, UK) was used to draw forest plots. Begg's test and Egger's test were used to evaluate publication bias using STATA Version 12.0 (StataCorp LP, College Station, TX, USA). Statistical heterogeneity was assessed via the Q statistic and I^2 tests. P-values of $\leq$0.05 were considered to indicate statistical significance. If there were no publication bias and statistical heterogeneity, we used the Mantel–Haenszel methods under the fixed-effects model to assess the association between the *HLA-B*1502* allele and LTG-induced SJS/TEN.

Results

Study selection

A total of 78 records were identified by searching the databases. After the exclusion of duplicate papers (nine records), reviews, notes, editorials, and letters (50 records), records in which cases were not LTG-induced SJS/TEN in Han Chinese subjects (seven records), studies that did not report the association between the *HLA-B*1502* allele and SJS/TEN (eight records), four studies remained, which were then included in the meta-analysis[10–13] (Fig. 1).

Study characteristics

The characteristics of the studies included are shown in Tables 1 and 2. The four studies included were case–control studies and referred to a total of 12 SJS/TEN patients and 128 matched control subjects (LTG-tolerant controls). There were no other obvious causes or drugs associated with the disease. All of the studies had been conducted in Han Chinese subjects. Scores on the NOS for the included studies ranged from 5 to 6.

Meta-analysis results

The quantitative meta-analysis indicated that there was a statistically significant association between the *HLA-B*1502* allele and LTG-induced SJS/TEN (OR: 4.98, 95% CI 1.43–17.28; P = 0.01). The forest plot is shown in Figure 2. Beggs and Eggers tests showed there to be no statistically significant publication bias (Eggers test for bias, P = 0.807; Beggs test for bias, P = 0.734). No statistically significant heterogeneity was detected based on I^2 (I^2 = 0.0%) and Q statistics (P = 0.66).

Discussion

In this meta-analysis, we found that the association between the *HLA-B*1502* allele and LTG-induced SJS/TEN was statistically significant. The *HLA-B*1502* allele increased the risk for SJS/TEN in patients using LTG. The risk for SJS/TEN in individuals using LTG and carrying this allele was 4.98 times greater than that of patients without the *HLA-B*1502* allele.

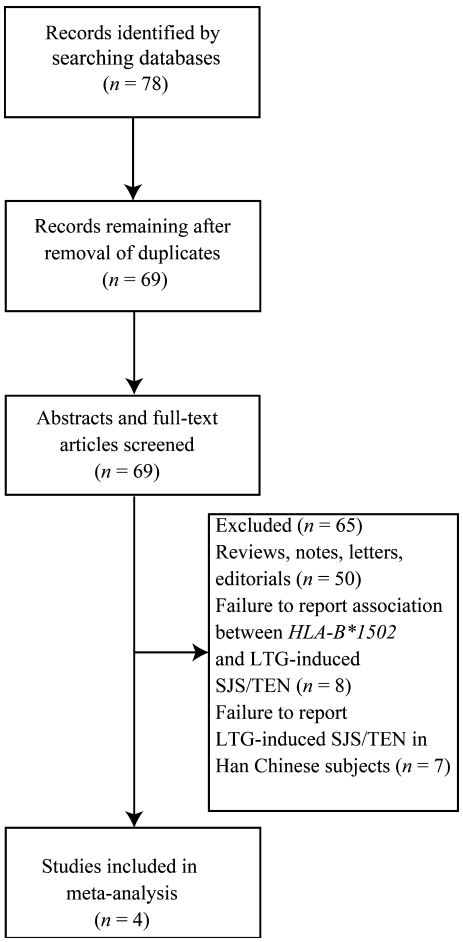

Figure 1 Flow diagram showing the selection of studies. LTG, lamotrigine; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

Previous studies[10–13] failed to find evidence of an association between the *HLA-B*1502* allele and LTG-induced SJS/TEN. This study is inconsistent with these previous results. There are various factors that may be responsible for the discrepancy. Firstly, because of their small sample sizes, the statistical power of each of these studies was too low to detect a statistically significant effect. Secondly, other genetic factors may also be associated with the occurrence of LTG-induced SJS/TEN.

The occurrence of SJS/TEN induced by aromatic AEDs such as CBZ and PHT was found to be associated with the *HLA-B*1502* allele. The strong association between the *HLA-B*1502* allele and CBZ-induced SJS/TEN was first reported in Taiwan (OR: 2504)[8] and was then confirmed by subsequent studies in Han Chinese,[10,17–21] Thai,[22,23] Malay,[24] and Indian[25] populations (ORs: 47.67–1357).[25] However, studies in some Asian populations, such as Japanese[26–31] and Koreans,[32] and in White Europeans[33] did not find any association between *HLA-B*1502* and CBZ-induced SJS/TEN. This may reflect different allele frequencies among these populations: the prevalence of *HLA-B*1502* is higher in the Malay (0.12–0.157), Han Chinese (0.057–0.145), and Thai (0.085–0.275) populations. By contrast, the frequency of *HLA-B*1502* is much lower in White European (0.01–0.02), Japanese (0.002), and Korean (0.004) populations.[34] On the basis of such data, the US Food and Drug Administration recommends genotyping this allele in Asians before prescribing CBZ.[35] In addition, recent studies have demonstrated an association between PHT-induced SJS/TEN and the presence of the *HLA-B*1502* allele in Han Chinese[11,12,36,37] and Thai[38] populations (ORs: 5.1–18.5).[38]

To date, only six studies have examined the association of the *HLA* gene with LTG-induced SJS/TEN. The four studies included in this meta-analysis found an association between *HLA-B*1502* and LTG-induced SJS/TEN in Han Chinese subjects (ORs: 1.13–21.00).[10–13] The other two studies found no instance of the *HLA-B*1502* allele in White European populations.[9,39] Furthermore, one of the two studies showed a weak association between *HLA-B*38* and LTG-induced SJS/TEN in a limited number of patients.[9] The other failed to find a single major HLA-related genetic risk factor in patients with LTG-induced SJS/TEN.[39] Only suggestive evidence was obtained for *HLA-B*5801*, *A*6801*, *CW*0718*, *DQB1*0609*, and *DRB1*1301*.[39]

Table 1 Characteristics of included studies

		LTG-induced SJS/TEN patients		LTG-tolerant patients		
Study	**Study design**	***HLA-B*1502* positive, *n***	**Total, *n***	***HLA-B*1502* positive, *n***	**Total, *n***	**NOS**
Man *et al.*[11]	Case–control	1	1	1	11	6
An *et al.*[10]	Case–control	1	3	1	21	6
Hung *et al.*[12]	Case–control	2	6	6	67	6
Shi *et al.*[13]	Case–control	0	2	4	29	5

LTG, lamotrigine; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NOS, Newcastle–Ottawa Scale.

Table 2 Demographic information in the included studies

Study	Study design	Male : female ratio		Mean age, years		Mean drug exposure, mg/d	
		LTG-induced SJS/TEN patients	LTG-tolerant patients	LTG-induced SJS/TEN patients	LTG-tolerant patients	LTG-induced SJS/TEN patients	LTG-tolerant patients
Man *et al.*[11]	Case–control	1 : 1	4 : 7	36	40	NA	NA
An *et al.*[10]	Case–control	1 : 2	9 : 12	25.3 ± 9.2	22.9 ± 8	66.7 ± 28.9	NA
Hung *et al.*[12]	Case–control	4 : 2	39 : 28	23.7	33.2	175	297.4
Shi *et al.*[13]	Case–control	0 : 1	NR	41	18.9	NA	NA

LTG, lamotrigine; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NR, not reported; NA, not available.

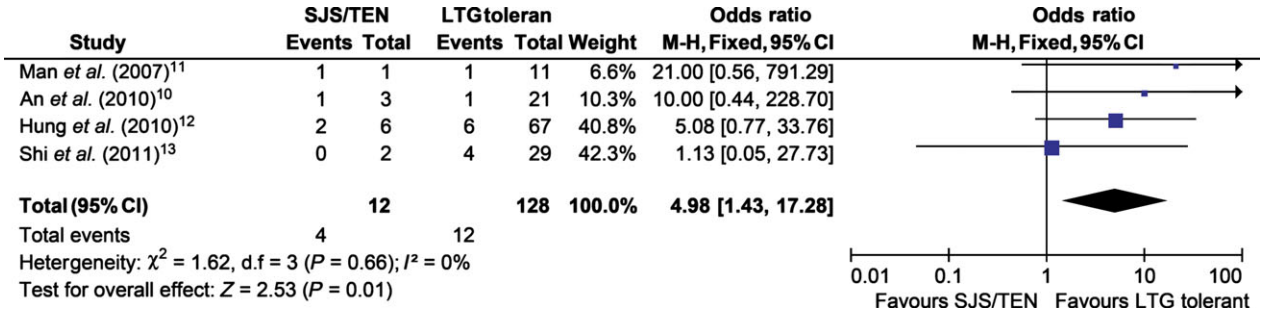

Figure 2 Forest plot for *HLA-B*1502* alleles and lamotrigine (LTG)-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). M-H, Mantel–Haenszel methods; 95% CI, 95% confidence interval

The association of the *HLA-B*1502* allele with LTG-induced SJS/TEN (OR: 4.98) is not as strong as that in CBZ-induced SJS/TEN (ORs: 47.67–1357). This may be explained by drug-specific factors and the existence of other genetic factors (other *HLA* alleles and genes encoding metabolic enzymes).[9,33,39] However, given the evidence that the *HLA-B*1502* allele is a common risk allele for the induction of SJS/TEN by aromatic AEDs[12] and the high rate of mortality in SJS/TEN,[3,6,40] the association between the *HLA-B*1502* allele and LTG-induced SJS/TEN is noteworthy. As LTG-induced SJS and TEN represent life-threatening severe adverse cutaneous reactions, we should be alert to the presence of the *HLA-B*1502* allele before prescribing LTG.

This meta-analysis is subject to some limitations. Firstly, although no statistically significant publication bias was found, it is possible that some measure of publication bias existed. Secondly, the sample size in each of the studies included in the analysis was small: even when pooled, the data included only 12 SJS/TEN patients. As the frequency of the *HLA-B*1502* allele is inconsistent across different populations, none of 22 patients with LTG-induced SJS/TEN in a European population study were found to carry the *HLA-B*1502* allele.[9] Thus, the association of the *HLA-B*1502* allele with LTG-induced SJS/TEN may be ethnicity-specific. Further investigations in larger, multicenter studies, in populations of the same ancestry, are required to confirm this association.

Conclusions

In this meta-analysis, we found a statistically significant association between the *HLA-B*1502* allele and LTG-induced SJS/TEN. Future studies with larger sample sizes are required to verify the results.

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