Systematic Review and Meta-Analysis

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HLA-A*24:02 associated with lamotrigine-induced cutaneous adverse drug reactions

A systematic review and meta-analysis

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Abstract

Background: Several studies demonstrated a connection between human leukocyte antigen (HLA)-B*1502 and lamotrigine (LTG)-induced cutaneous adverse drug reactions (cADRs). The correlation between the HLA-A*24:02 and LTG-cADRs remains controversial. To examine the associations between HLA-A*24:02 and LTG-cADRs, we conducted a systematic review and meta-analysis.

Methods: We performed a comprehensive search of the literature in several electronic database systems including Cochrane Library, EMBASE and PubMed from inception to January 2020. Review Manager was used to compare the frequencies of HLA-A*24:02 carriers between the subgroups.

Results: A total of 5 studies were eligible, including 197 LTD-cADRs, 396 LTD-tolerant controls, and 2068 population controls. Compared with the LTG-tolerant controls, there was a statistically significant association between the HLA-A*24:02 allele and LTG-induced cADRs (odds ratios: 1.94, 95% confidence intervals 1.06–3.54; $P = .03$). Compared with the general population, the relationship between the HLA-A*24:02 genotype and LTG-induced cADRs was statistically significant (summary odds ratios: 2.12, 95% confidence intervals 1.04–4.30; $P = .04$).

Conclusions: HLA-A*24:02 may be a risk factor for LTG-cADRs.

Abbreviations: AEDs = antiepileptic drugs, cADRs = cutaneous adverse drug reactions, CIs = confidence intervals, EP = Epilepsy, HLA = human leukocyte antigen, LTG = lamotrigine, MPE = mild maculopapular exanthema, ORs = odds ratios, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

Keywords: cutaneous adverse drug reactions, human leukocyte antigen-A*24:02, lamotrigine, meta-analysis

1. Introduction

Epilepsy (EP) is a neurological disease characterized by repeated seizures, that can be successfully controlled or treated with long-term antiepileptic drugs (AEDs) in most patients.[1] Common AEDs include valproate, carbamazepine, lamotrigine (LTG), and oxcarbazepine.[2,3] Cutaneous adverse drug reactions (cADRs) are frequently reported side effects in patients taking AEDs that contain aromatic rings. The incidence of AED-induced cADRs was estimated at 3.61%.[4] CADRs can be divided into 2 categories: bullous lesions and nonbullous reactions.[5] Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are cADRs characterized by bullous lesions,[6] while mild maculopapular exanthema (MPE) and drug hypersensitivity syndrome (HSS) are characterized by nonbullous reactions.[5] Drug discontinuation due to AED-ADRs occurs frequently in EP patients, resulting in poor control. Although rare (1:1000–1:10000), 10% to 40% mortality rates has been reported in patients with SJS and TEN.[7–9]

Pharmacogenomics studies have identified a strong link between human leukocyte antigen (HLA) markers and AED-induced cADRs. Several studies have demonstrated associations between HLA-B*15:02 and LTG-induced SJS/TEN.[10,11] The HLA-A*31:01 allele is a genetic risk factor for LTG-induced severe cutaneous adverse reactions in the Korean population.[12] HLA-A*24:02 was found to be a protective marker against bullous skin reactions in Asian patients treated with carbamazepine.[5] A case-control study[13] showed that HLA-A*24:02 was a risk factor for cADRs caused by aromatic AEDs in the south Chinese Han population as well as in others.

Many studies[12,14,15] have examined correlations between HLA-A*24:02 and LTG-cADRs, with conflicting results. Meta-analysis can help determine correlations by combining statistics from various studies. To predict the possibility of adverse skin reactions in epileptic patients taking LTG, we performed a meta-analysis of case-control studies in European and Asian patients with EP using LTG.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2. Methods

2.1. Information sources and literature searches

The meta-analysis was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses[16] recommendations. We performed a comprehensive search of the Cochrane Library, EMBASE and PubMed from inception to January 2020. The search terms used were as follows: "human leukocyte antigen" or "HLA Antigens" or "Antigens, HLA" or "HLA" and "lamotrigine" or "LTG" or "Lamictal" or "Lamiktal" or "BW430C" or "Labileno" and "cutaneous adverse reaction" or "skin reaction" or "Stevens-Johnson Syndrome" or "SJS" or "toxic epidermal necrolysis" or "TEN" or "maculopapular eruption" or "maculopapular rash" or "MPE" or "hypersensitivity syndrome" or "HSS" or "skin reactions" or "drug reaction". The language of the included studies was English only. We also searched references of relevant papers so as to obtain other pertinent studies. We did not consider unpublished papers or articles without full text.

2.2. Inclusion and exclusion criteria

Two reviewers (JW and HJ L) independently reviewed titles, abstracts, and full articles retrieved from the comprehensive search. Studies were included if they conformed to all of the following criteria:

(1) HLA-A*24:02 was determined;
(2) papers were retrospective studies or case-control studies;
(3) cADRs were induced by LTG; and
(4) sufficient data were given to calculate the frequency of HLA-A*24:02 carriers among cases and controls.

The exclusion criteria were follows:

(1) case reports or case series;
(2) duplicate publication;
(3) review articles or meeting papers; and
(4) patients receiving other AEDs for EP.

2.3. Data extraction and quality assessment

Two investigators (JW and HJ L) independently extracted all data from each study, and discrepancies were resolved by discussion. The following characteristics were extracted: study, publication year, nationality, control study, the ratio of positive numbers, and scores of Newcastle-Ottawa Quality Assessment Scale. If insufficiently detailed content were reported, the desired information was obtained from the articles. Otherwise, the authors were called to obtain the required information.

Comparisons of the frequencies of HLA-A*24:02 carriers between the subgroups were carried out using Review

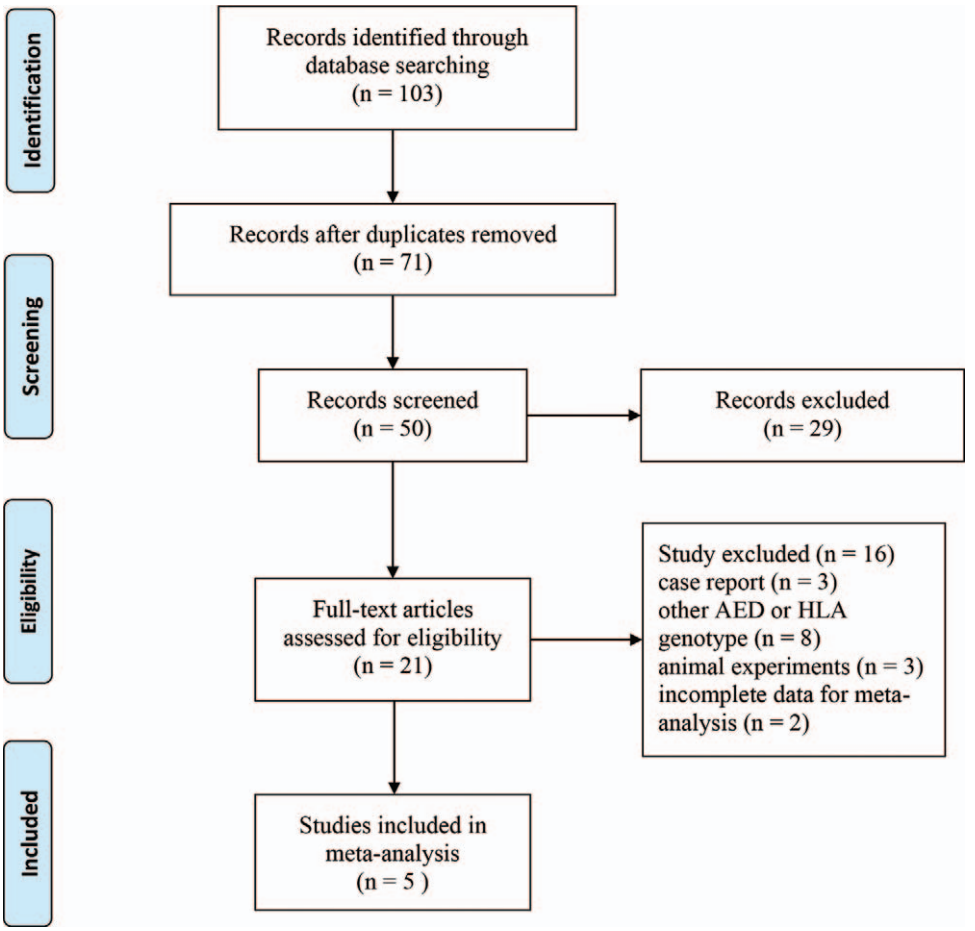

Figure 1. Flow diagram for eligible studies.

Table 1

Characteristics of studies included in the meta-analysis.

Source	Nationality	Control	No. positive for HLA-A*24:02/Total No.		NOS
			Case	Tolerant control	
Moon et al, 2015	Korean	tolerant and population	15/21 MPE	12/29	5
Li et al, 2013	Han-Chinese	tolerant and population	14/43 MPE	18/44	6
Shirzadi et al, 2015	Norwegian	tolerant and population	10/28 cADRs	13/90	6
Shi et al, 2017	Han-Chinese	tolerant	10/22 SJS/TEN		
13/55 MPE	16/102	5			
Kim et al, 2017	Korean	tolerant	11/28 SCAR	11/29	5

cADRs = cutaneous adverse drug reactions, HLA = human leukocyte antigen, MPE = mild maculopapular exanthema, NOS = Newcastle-Ottawa Quality Assessment Scale, SCAR = severe cutaneous adverse reactions, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

Manager (version 5.3), and a *P*-value of $< .05$ was considered to indicate statistical significance. Haldane's modification was used to calculate odds ratios (ORs). The ORs and their corresponding 95% confidence intervals (CIs) were calculated using Haldane's modification to compare the frequencies of HLA-A*24:02 carriers between the subgroups (case and tolerant groups). ORs with CIs were pooled using a fixed-effects model or a random-effects model. If heterogeneity was not present among the studies ($P > .5$, $I^2 < 50\%$), the fix-effects model was adopted.[17] If heterogeneity was shown ($P < .05$ or $I^2 > 50\%$), the random-effects model was adopted.[18]

2.4. Ethical approval

No ethical approval was necessary because our meta-analysis was performed based on data extracted from previous studies that had been approved and published.

3. Results

3.1. Study selection

A total of 103 documents [EMBASE (n = 63), PubMed (n = 40), the Cochrane Library (n = 0)] were identified according to the inclusion criteria. A total of 32 duplicated articles and 29 irrelevant studies were excluded. Then, case reports (n = 3), other AEDs or HLA genotypes (n = 8), animal experiments (n = 3) or papers with insufficient data for meta-analysis (n = 2) from the 16 articles were excluded by reading the complete texts. Finally, 5 case-control studies[12–15,19] were included in the meta-analysis. The flow chart is illustrated in Figure 1.

3.2. Study characteristics

Detailed characteristics of the pooled studies are shown in Table 1. Five included studies were case-control studies including a total of 197 patients with LTD-cADRs and 396 matched LTG-tolerant controls. CADRs outcomes were clearly defined in 3 of the 5 study. The study areas included Norway, Korea, and China. Newcastle-Ottawa Quality Assessment Scale scores for the pooled trials ranged from 5 to 6.

3.3. Association between HLA-A*24:02 and LTG-induced cADRs

A total of 197 LTG-induced cADRs and 396 tolerant-controls were involved in the 5 studies. As shown in Figure 2, there was a statistically significant association between the HLA-A*24:02 allele and LTG-induced cADRs (OR: 1.94, 95% CI 1.06–3.54; $P = .03$). A random-effects model was used for the high heterogeneity (I^2: 56%, $P = .04$) across the 5 included studies.

Four studies[12,14,15,19] with 110 patients and 2068 population-controls were included to test the relationship between the HLA-A*24:02 genotype and LTG-induced cADRs (Fig. 3). Compared with the general population, the relationship between the HLA-A*24:02 genotype and LTG-induced cADRs was statistically significant (summary OR: 2.12, 95% CI 1.04–4.30; $P = .04$). Because heterogeneity was high (I^2: 62%, $P = .05$), a random-effects was chosen to analyze the studies.

3.4. Publication bias

There was no evidence of publication bias among the included studies, according to the funnel plots (Fig. 4).

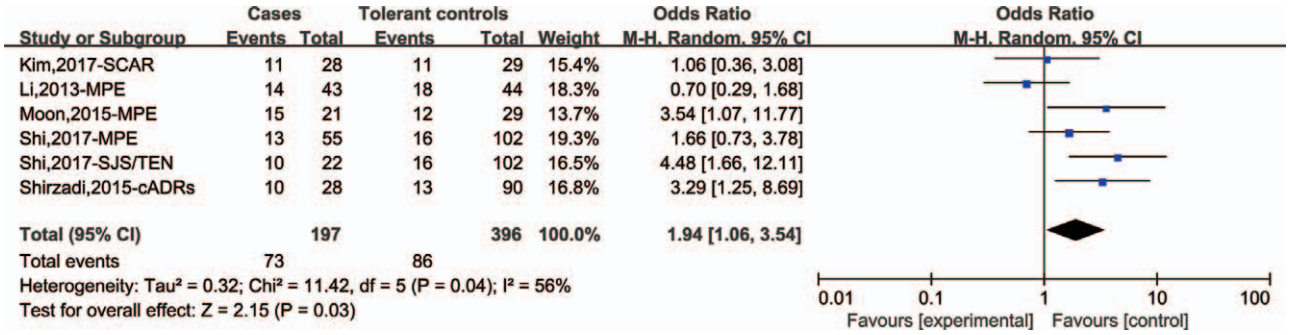

Figure 2. Forest plot of human leukocyte antigen-A*24:02 association with lamotrigine-induced cutaneous adverse drug reactions (lamotrigine-induced cutaneous adverse drug reactions versus tolerant group).

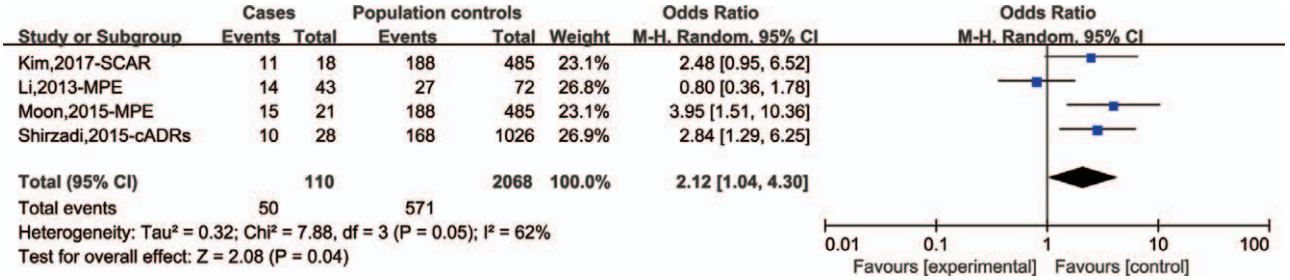

Figure 3. Forest plot of human leukocyte antigen-A*24:02 association with lamotrigine-induced cutaneous adverse drug reactions (lamotrigine-induced cutaneous adverse drug reactions versus population control group).

4. Discussion

In this meta-analysis, we found that HLA-A*24:02 directly correlated with LTG-induced cADRs. The risks for cADRs in individuals using LTG and carrying HLA-A*24:02 were 1.94 and 2.12 times higher than that of tolerant-control and population-control patients, respectively.

Shizadi et al found that HLA-A*24:02 was significantly associated with LTG-induced cADRs.[14] Kim et al found that the frequency of HLA-A*24:02 was higher in patients with LTG-induced cADRs than in an LTG-tolerant group.[12] Li et al founded that the allele HLA-A*24:02 was not a major risk factor in LTG-induced MPE.[15] Our meta-analysis of these studies verified increased susceptibility to cADRs in populations carrying HLA-A*24:02.

CADRs such as SJS, TEN and drug rashes with eosinophilia and systemic symptoms are considered severe cADRs, while MPE and bullous firm drug rashes are considered non-severe.[20] The heterogeneity is higher than 50%, possibly related to racial differences or different cADRs. In this meta-analysis, only 5 references were included, making it difficult to conduct subgroup analysis. For example, another HLA allele (HLA-B*15:02) was related to SJS/TEN and MPE; the ORs for carriers of HLA-B*15:02 using LTG were approximately 2.52-fold higher for SJS/TEN and there was no significant difference for TEN.[21]

Although the mechanism by which HLA-A*24:02 contributes to cADRs among LTG users is not completely understood, it is recognized that HLA molecules provide exogenous or endogenous antigens to T cells.[22] T-cell receptors are thought to identify antigens provided by specific HLA-A molecules on antigen-presenting cells, resulting in release of inflammatory mediators and strong immune reactions in cADRs.[23–25]

There are several limitations in the current meta-analysis. First, this study investigated only the relationship between HLA-A*24:02 allele and LTG- induced cADRs. Other HLA alleles that may be associated with cADRs were excluded. Second, the numbers and sample sizes included were small: only 5 case-control studies with 197 LTG-cADRs were pooled in the meta-analysis. More large-scale studies are warranted to validate our conclusions. Because of the small number of studies, subgroup analysis was not performed. With continued research, larger numbers of high-quality studies can be included in subgroup analyses. Finally, 4 included studies were conducted in Asian and European; more studies are required in different ethnic groups.

Despite these limitations, our meta-analysis was the first systematic review to evaluate the associations between HLA-A*24:02 and LTG-cADRs. Our study showed that HLA-A*24:02 was a risk factor for developing cADRs in patients taking LTG. LTG should be prescribed with caution in patients with known presence of HLA-A *24:02. Detecting HLA-A genes may help us to make better predictions regarding the possibility for generating cADRs in patients prior to taking LTG.

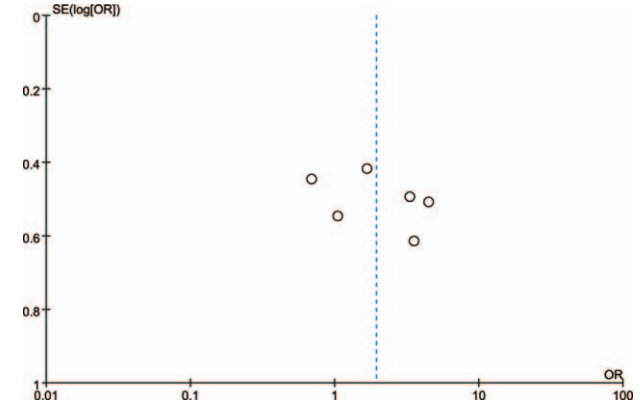

Figure 4. Funnel plot of human leukocyte antigen-A*24:02 association with lamotrigine-induced cutaneous adverse drug reactions (lamotrigine-induced cutaneous adverse drug reactions versus tolerant group).

5. Conclusions

There is a statistically significant association between the HLA-A*24:02 allele and LTG-induced cADRs.

Author contributions

Methodology: Jie Wang, Hangjuan Lin.
Project administration: Jie Wang, Hangjuan Lin.
Software: Wanshu Li.
Writing – original draft: Wanshu Li.
Writing – review & editing: Gang Shen.

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