ASSOCIATIONS BETWEEN *HLA* GENOTYPES AND DAPSONE-METHAZOLAMIDE-OXCARBAZEPINE INDUCED ADVERSE DRUG REACTIONS USING SYSTEMATIC REVIEW AND META-ANALYSIS TECHNIQUE

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A Thesis Submitted to the Graduate School of Naresuan University
in Partial Fulfillment of the Requirements
for the Doctor of Philosophy Degree in Pharmaceutical Sciences
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Thesis entitled "Associations between *HLA genotypes* and dapsone-methazolamide-oxcarbazepine induced adverse drug reactions using systematic review and meta-analysis technique"

by Wimonchat Tangamornsuksan

has been approved by the Graduate School as partial fulfillment of the requirements for the Doctor of philosophy Degree in Pharmaceutical Sciences of Naresuan University

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Wimonchat Tangamornsuksan

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) are a source of significant morbidity and mortality in healthcare systems. It has been estimated that approximately 6.7% of hospital admissions are caused by ADRs and 2% of the patients admitted with an adverse drug reaction died. Severe cutaneous adverse drug reactions (cADRs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening reactions. Both SJS and TEN are characterized by blisters arising on purple macules on the lips, eyes, mouth, genitals and airways. The skin detachment percentage differentiates SJS (less than 10%), SJS/TEN overlap (between 10%-30%) and TEN (more than 30%). Despite relatively low incidence of SJS (1.2-6 cases per million persons per year) and TEN (0.4-1.2 cases per million persons per year) mortality rates of SJS and TEN are relatively high (4.8% for SJS, 19.4% for SJS/TEN overlap and 14.8% for TEN). Although, several studies suggested that genetic predisposition plays a significant role in ADRs. Human leukocyte antigen

(HLA) genotypes are a family of genes involving immune reactions. Associations between *HLA* genotypes and drug-induced SJS/TEN are well-established. *HLA* genotypes are the most polymorphic gene cluster in the human genome. Specific polymorphisms in *HLA* genotypes are associated with various ADRs, for example the associations between *HLA-B*5801* and allopurinol-induced SJS/TEN, *HLA-B*5701* and abacavir-induced hypersensitivity, *HLA-B*1502* and carbamazepine-induced SJS/TEN, *HLA-B*1502* and oxcarbazepine-induced SJS/TEN. Many several reports regarding use of dapsone, methazolamide and oxcarbazepine and *HLA* genotypes may be associated with increased risks in developing cADRs. However, a major limitation of the individual studies is the low incidence of the drugs-cADRs. Small sample sizes among those studies may contribute observed variations. Nonetheless, risks in developing cADRs of people carrying the *HLA* genotypes in different ethnicities might be different. An important part of reducing cADRs is an understanding of population risks as well as HLA genotyping before drug treatment. Therefore, to better assess these risks, we aimed to review all relevant studies and to quantitatively synthesize the magnitude of the associations between dapsone-induced, methazolamide-induced, and, oxcarbazepine-induced cADRs and certain *HLA* genotypes using a systematic review and meta-analysis technique.

Methods: We searched for studies investigating the association between *HLA* genotypes and dapsone, methazolamide, and, oxcarbazepine-induced ADRs and providing sufficient information on frequency of carriers of *HLA* genotypes among cases and controls. Meta-analysis with a random-effects model was performed.

Results: There were 3, 2 and 5 studies included in our meta-analysis for dapsone, methazolamide, and, oxcarbazepine, respectively. Association between *HLA-B*1301* and dapsone-induced cADRs was identified (summary OR=43.0; 95%CI=24.0-77.2). In subgroup analyses among types of cADRs similar findings were found in dapsone-induced hypersensitivity (OR=51.7; 95%CI=16.9-158.5), dapsone-induced severe cADRs (SJS/TEN plus drug rash with eosinophilia and systemic symptoms [DRESS]) (OR=54.0; 95%CI=8.0-366.2). Associations between *HLA-B*1502* and oxcarbazepine -induced SJS were found in both the general population [OR=30.2 (95%CI=3.45-264)] and in oxcarbazepine-tolerant individuals [OR=26.4 (95%CI=7.98-87.6)]. In addition, an association between the *HLA-B*1502*

and oxcarbazepine-induced maculopapular rash was found in the general population [OR=5.67 (95%CI=2.03-15.9)] while *HLA-A*3101* also associated with oxcarbazepine-induced maculopapular rash [overall OR=29.2 (95%CI=6.70-128)]. Associations between *HLA-B*5901*, *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were identified in methazolamide-tolerant and population controls. Summary ORs were 305.0 (95%CI=11.3-8,259.4) in methazolamide-tolerant and 715.3 (95%CI=83.1-6,158.5) in population control. Associations between the *HLA-Cw*0102* and methazolamide-induced SJS/TEN were found in methazolamide-tolerant (OR=12.1; 95%CI=1.3-111.7) and population control (OR=17.5; 95%CI=3.2-96.6).

Conclusions: Since, the associations between *HLA-B*1301* and dapsone-induced cADRs, *HLA-B*5901*, *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN, and *HLA-B*1502* and oxcarbazepine-induced cADRs were identified in our study. To ensure safety of the drugs treatments with 3 therapeutic agents, genetic screening among susceptible population prior to starting drug treatments is warranted.

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ABBREVIATIONS

ADRs	=	adverse drug reactions
ALDEN	=	Algorithm of drug causality for epidermal necrolysis
APCs	=	antigen-presenting cells
BFDE	=	bullous fixed drug eruption
cADRs	=	cutaneous adverse drug reactions
CI	=	confidence intervals
DRESS	=	drug rash with eosinophilia and systemic symptoms
DHS	=	Dapsone-induced hypersensitivity syndrome
HLAs	=	human leukocyte antigens
HuGENet	=	Human Genome Epidemiology Network
HWE	=	Hardy-Weinberg equilibrium
MHC	=	major histocompatibility complex
NOS	=	The Newcastle-Ottawa scale
OR	=	odds ratio
OXC	=	oxcarbazepine
PCR	=	polymerase chain reaction
SJS	=	Stevens-Johnson syndrome
TEN	=	toxic epidermal necrolysis

CHAPTER I

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening hypersensitivity reactions [1, 2, 3]. Both SJS and TEN are characterized by blisters arising on purple macules on the lips, eyes, mouth, genitals and airways [2, 3]. The skin detachment percentage differentiates SJS (less than 10%), SJS/TEN overlap (between 10%-30%) and TEN (more than 30%) [4]. Despite relatively low incidence of SJS (1.2-6 cases per million persons per year) [5, 6, 7] and TEN (0.4-1.2 cases per million persons per year) [5, 6, 7, 8]. Mortality rates of SJS and TEN are relatively high (4.8% for SJS, 19.4% for SJS/TEN overlap and 14.8% for TEN) [2]. Medication (e.g., sulfonamides, antiepileptic drugs, allopurinol) and genetic predisposition play a significant role in SJS/TEN [9, 10]. Human leukocyte antigen (HLA) genotypes are a family of genes involving immune reactions which located on chromosome 6 in humans [8, 11]. MHC are cell-surface receptors that capture and present self- and pathogen-derived peptides to T-cell receptor. Associations between *HLA* genotypes and sulfonamides-induced SJS/TEN are well-established [9, 12, 13]. *HLA* genotypes are the most polymorphic gene cluster in the human genome [8, 11]. Specific polymorphisms in *HLA* genotypes are associated with various adverse drug reactions, for example the associations between *HLA-B*5801* and allopurinol-induced SJS/TEN [14], *HLA-B*5701* and abacavir-induced hypersensitivity [15], *HLA-B*1502* and carbamazepine-induced SJS/TEN [16].

The associations between *HLA* genotypes and dapsone [17, 18, 19]-methazolamide [13, 20, 21, 22, 23, 24, 25, 26, 27]-oxcarbazepine [28, 29, 30, 31] induced adverse drug reactions were investigated in some epidemiological studies. However, these previous studies have shown considerable variation among *HLA* genotypes, types of adverse drug reactions (i.e., maculopapular rash, SJS/TEN) and magnitude of the associations. A major limitation of the individual studies is the low incidence of the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine)-

induced adverse drug reactions, and thus small sample sizes may be attribute to this observed variation.

An important part of reducing adverse drug reactions is an understanding of populations at risk (or genetically predisposed populations) as well as HLA genotyping before drug treatment. Therefore, to better assess these risks, review all relevant studies and to quantitatively synthesize the magnitude of the associations using a systematic review and meta-analysis technique. Meta-analytic technique is frequently used to combine and analyze finding. This systematic approach can increase power, improve precision and elucidate potential similarities and differences that would explain the findings from relevant studies.

Research aim

To systematically review and quantitatively assess associations between certain *HLA* genotypes and adverse drug reactions induced by 1) dapsone, 2) methazolamide, and; 3) oxcarbazepine using systematic review and meta-analysis technique

Research hypothesis

There is an association(s) between certain *HLA* genotypes and dapsone-methazolamide-oxcarbazepine induced adverse drug reactions. The differences in associations between *HLA* genotypes and dapsone-methazolamide-oxcarbazepine induced adverse drug reactions among relevant studies are resulted from different types of control (e.g., tolerant controls or healthy controls) and/or studies design and/or ethnicity and/or diagnostic method of adverse drug reactions.

Research scope

To determine the associations between *HLA* genotypes and dapsone-methazolamide-oxcarbazepine induced adverse drug reactions, study design, language of studies, type of adverse drug reactions and *HLA* genotypes are not restricted. However, comprehensive and systematic searches will be performed in PubMed/Medline (U.S. National Library of Medicine, Bethesda, MD, USA),

HuGENet (Human Genome Epidemiology Network), and Cochrane library, using the keywords, synonyms and other terms related to *HLA* genotypes and the drugs of interest(i.e., dapsone, methazolamide and oxcarbazepine). Only published, peer-reviewed, original research articles from will be included in this study.

Limitations

A meta-analysis will be performed when *HLA* genotypes and/or types of adverse drug reactions induced by the targeted drugs (i.e., dapsone, methazolamide and oxcarbazepine) have been documented in two or more separate studies and have sufficient data for conducting the analysis.

In addition, since our analyses were performed based on available information, thus small numbers of the included studies and small sample size effects could not be avoided. Due to these effects, some limitations may exist and result in 1) higher level of heterogeneities; 2) publication bias; and, 3) tendency of results.

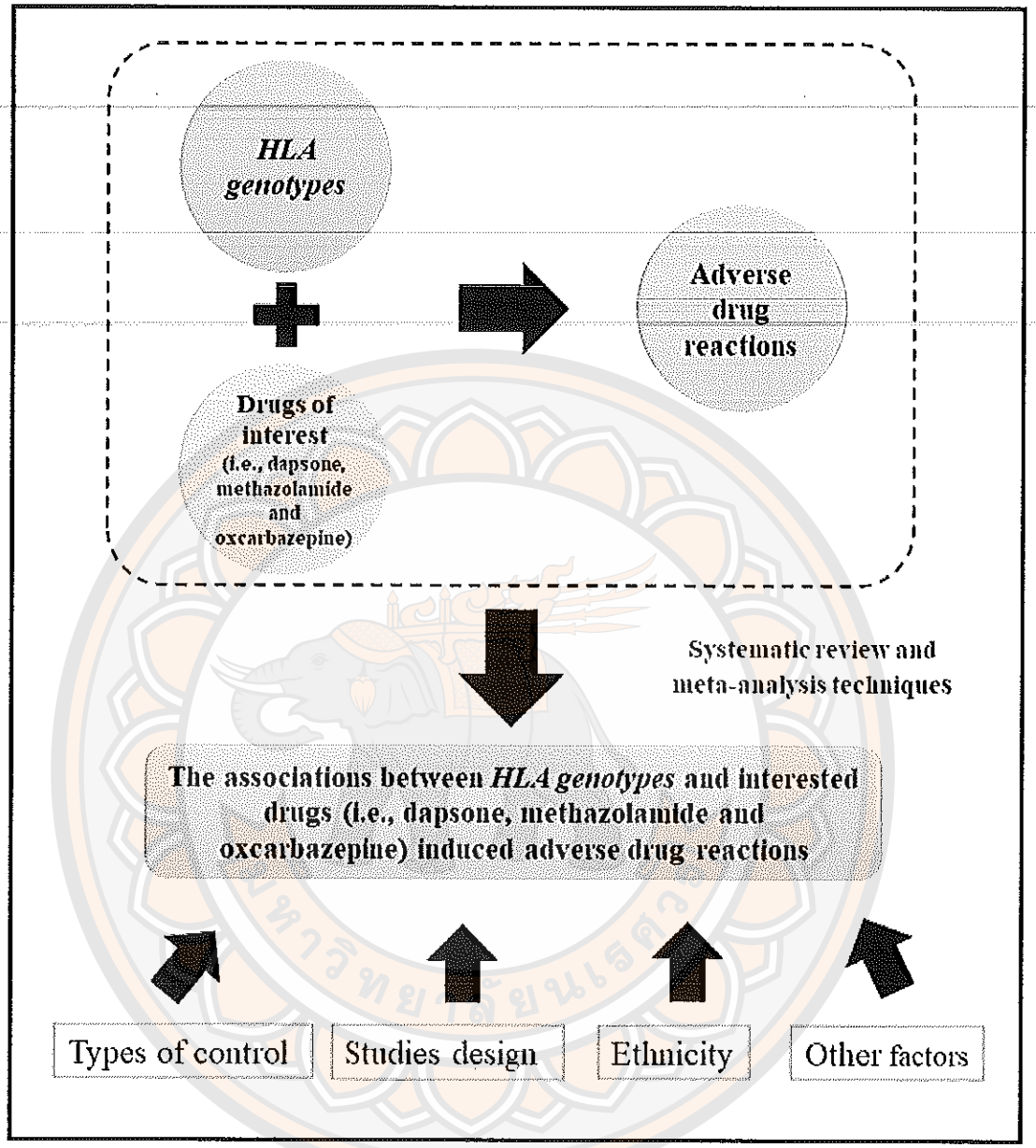

Figure 1 Conceptual framework of associations between *HLA* genotypes and dapsone-methazolamide-oxcarbazepine induced adverse drug reactions using systematic review and meta-analysis technique

CHAPTER II

LITERATURE REVIEW

Human leukocyte antigen

The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, is located on chromosome 6. It encodes cell-surface receptors that capture and present self- and pathogen-derived peptides to T cells receptor (TCR). HLA is divided into 3 groups, HLA Class I, II and III, Nonetheless, only HLA Class I and II are associated with drug induced adverse drug reactions (ADRs) [8, 32, 33, 34].

HLA Class I consists of α heavy chain, composed of three domains α_1, α_2 and α_3. This heavy chain is bound to a β_2-microglobulin molecule. The heavy chain consists of 2 peptide-binding domains, an Ig-like domain, and a transmembrane region with a cytoplasmic tail (Figure 2). HLA Class I is divided into 3 major groups, HLA-A, HLA-B, and HLA-C. The proteins products of these genes are present on the surface of almost all cells. On the cell surface, these proteins are bound to protein fragments (peptides) that have been exported from the cell. MHC class I proteins display these peptides to the immune system ($CD8^+$). If the immune system recognizes the peptides as foreign entities (such as viral or bacterial peptides); it responds by triggering a self-destruction process of the infected cell [8, 33, 34].

HLA Class II consists of 2 α heavy chain and 2 β_2-microglobulin molecule. Each chain has a peptide-binding domain, an Ig-like domain, and a transmembrane region with a cytoplasmic tail (Figure 2). There are six main HLA class II genes in humans, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1. They are usually present on antigen-presenting cells (APCs) (i.e., B cells, macrophages, dendritic cells, and Langerhans cells), thymic epithelium, and activated T cells [8, 34].

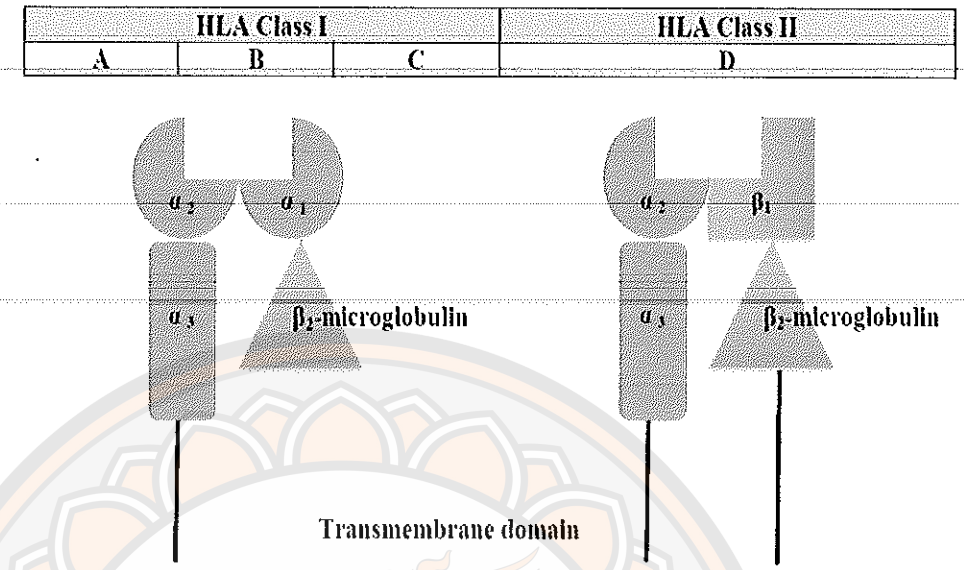

Figure 2 HLA class I and HLA class II molecule

Source: Adapted from Abbas, et al. [35]

Dapsone

Dapsone is an antimicrobial and anti-inflammatory drug widely used in some diseases [36]. As an antimicrobial agent, dapsone has been used in treatment of leprosy, actinomycetoma, prophylaxis of *Pneumocystis carinii pneumonia*, and malaria. Nonetheless, it has been used in several dermatologic conditions (e.g., dermatitis herpetiformis, linear IgA dermatosis, and pustular psoriasis) [37, 38]. Adverse effects of dapsone are both pharmacological adverse effects (e.g., hemolytic anemia, methemoglobinemia, and agranulocytosis) and idiosyncratic adverse effects [Dapsone-induced hypersensitivity syndrome (DHS)] [36]. Idiosyncratic adverse effects of dapsone range from mild cutaneous reaction to severe life-threatening, such as exfoliated dermatitis, liver failure, agranulocytosis, Stevens-Johnson syndrome and toxic epidermal necrolysis, nephritis and renal failure [39, 40]. Dapsone-induced hypersensitivity syndrome is a life-threatening drug reaction with a mortality rate of

9.9-12.5% [41, 42, 43]. DHS is characterized by fever, rash and systemic involvement. It is usually manifested in first 6 weeks after dapsone initiation.

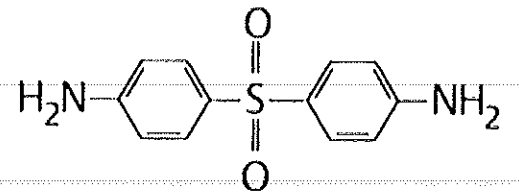

Figure 3 Structural formula of dapsone

Source: Wozel, et al. [38]

Methazolamide

Methazolamide is a carbonic anhydrase inhibitor. The drug is indicated in the treatment of increased intraocular pressure in chronic open-angled glaucoma and secondary glaucoma [44, 45]. Structurally, methazolamide has a sulfone group in its chemical structure (Figure 4), similarly to those of sulfonamide drugs (e.g., sulfamethoxazole, sulfisoxazole) [44]. Since methazolamide and sulfonamide drugs share a striking similarity in their chemical structures, it is possible that exposure to methazolamide may be able to induce SJS/TEN [46, 47, 48, 49, 50].

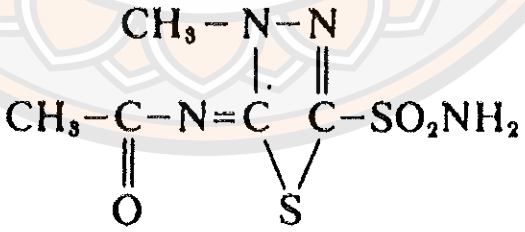

Figure 4 Structural formula of methazolamide

Source: Maren, et al. [44]

Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazepine (Figure 5) and approved as a monotherapy or adjunctive therapy to treat partial seizures in adults and children [51]. However, oxcarbazepine shows some similarities with carbamazepine. Their chemical structures. It has less severe cutaneous adverse drug reactions and thus may be a safer choice for carbamazepine-intolerant patients [52]. Oxcarbazepine induced cutaneous adverse drug reactions vary from mild maculopapular rash to severe reactions (i.e., Stevens-Johnson syndrome/toxic epidermal necrolysis, SJS/TEN), and drug rashes with eosinophilia and systemic symptoms with eosinophilia and systemic symptoms, DRESS). However, the most common oxcarbazepine induced cutaneous adverse drug reactions is maculopapular rash [53]. 25-78% of carbamazepine-induced hypersensitive patients develop a cross reaction with oxcarbazepine, while 29-40% of oxcarbazepine-induced hypersensitive patients cross react with carbamazepine [54, 55, 56].

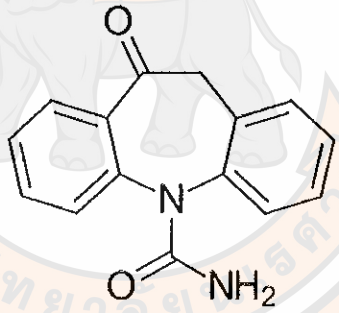

Figure 5 Structural formula of oxcarbazepine

Source: Kalis, et al. [51]

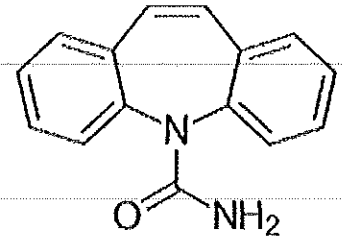

Figure 6 Structural formula of carbamazepine

Source: Kalis, et al. [51]

Systematic review and meta-analysis

Cochrane Handbook for Systematic Reviews of Interventions provided a definition of systematic review as follows: "A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made" [57].

The key of a systematic review are 1) clearly stated set of objectives with pre-defined eligibility criteria for studies, 2) an explicit, reproducible methodology, 3) a systematic search that attempts to identify all studies that would meet the eligibility criteria, 4) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and 5) a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

Cochrane Handbook for Systematic Reviews of Interventions [57] provided a definition of meta-analysis as follows:

The use of statistical methods to summarize the results of independent studies. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review. They also facilitate investigations of

the consistency of evidence across studies, and the exploration of differences across studies.

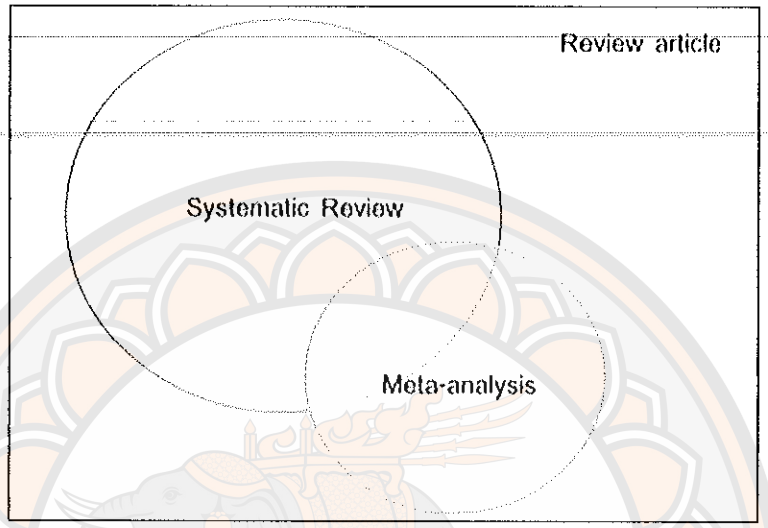

Figure 7 Types of review

Source: Adapted from Cochrane Handbook for Systematic Reviews of Interventions [57]

However, many systematic reviews do not contain meta-analyses. This depends on whether or not the included studies share sufficient similarities among the studies and combining their results is meaningful.

Based on systematic and reproducible process of systematic review and meta-analysis, these techniques can provide useful summary of the current scientific evidence on a specific topic. In addition, these also helps researchers to identify gaps of knowledge, ensure generalizability of the findings, and explain source of inconsistency finding of the included studies.

Steps in systematic review and meta-analysis

In brief, there are 5 essential steps of conducting systematic review and meta-analysis (Figure 8). More information regarding interpreting meta-analysis results can be found elsewhere [57, 58, 59].

1. **Defining research question**
2. **Searching for relevant studies**

Electronic databases and comprehensive search terms will be defined in this step. References list of review papers and communication with experts who have been working in the relevant field are important in this step. Search terms, specific databases and unpublished studies should be provided by experts. In addition, unpublished studies and non-English studies should not be restricted in this step.

3. **Selection of relevant studies**

Inclusion and exclusion criteria will set in this step to select relevant studies from the previous searching step. This step is generally done by at least two reviewers to determine inter-rater reliability. In this step, reviewers should ensure that there is no missing of relevant studies.

4. **Extracting data and assessing quality from included studies**

Important information (e.g., study design, characteristics of participants, outcome) from included studies will be extracted into organized tables. This step is also generally performed by at least two reviewers to determine inter-rater reliability and avoid data entry errors.

5. **Data synthesis**

Information in forth step will be combined, analyzed, and presented. This step can be done qualitatively using systematic review and quantitatively using statistical techniques, including meta-analysis. However, not all of systematic reviews can perform meta-analysis. Sometimes meta-analysis could not be sensibly to perform (e.g. different definitions of outcomes).

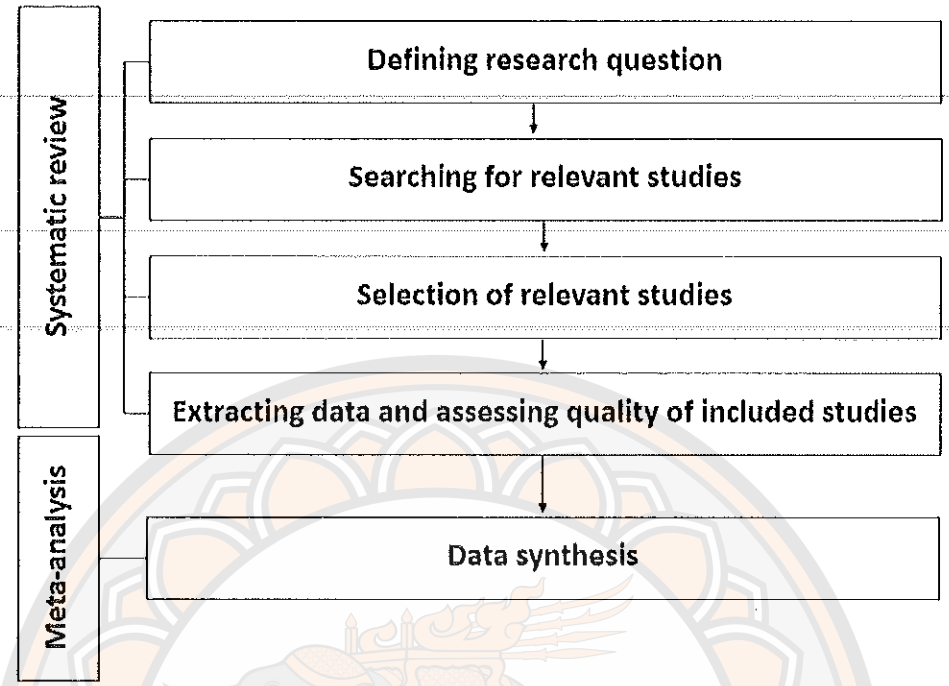

Figure 8 Steps of conducting systematic review and meta-analysis

Source: Adapted from Cochrane Handbook for Systematic Reviews of Interventions [57]

The results of meta-analysis is commonly reported in a Forest plot (Figure 9). The Forest plot provides graphical representations of meta-analysis result (summary result/pooled result) and results of individual studies.

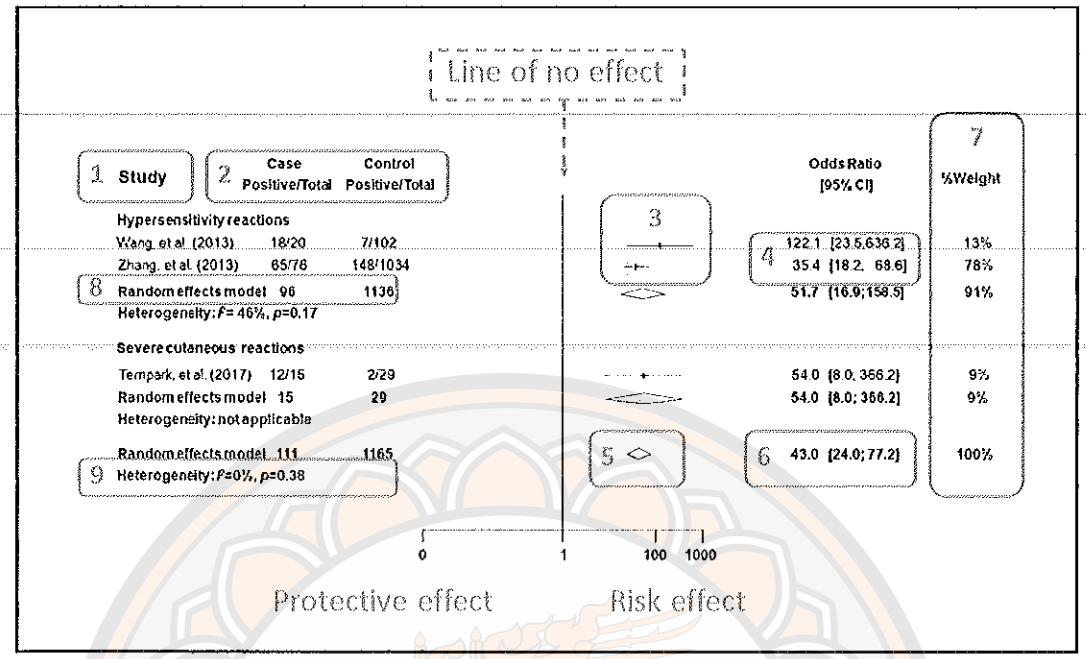

Figure 9 An example of a forest plot

How to read a forest plot [60]

1. **Study name:** Each included studies in meta-analysis will be represented by a line.

2. **Case/Control:** The number of subjects who exposed (carrying at least one allele of *HLA genotypes*) and the total number of subjects in each group will be reported in this part.

3. **Horizontal lines, black squares and grey boxes:** The confidence intervals of the effect estimate of each included studies will be represented by a horizontal lines. Black squares show the risk estimates of the included studies. While grey boxes indicate the sample size, 95% CI, and % weight from each included studies.

4. **Odds ratio (ORs):** Results of the individual studies will be reported by a line in term of ORs. ORs represent risk to develop outcome of interest in exposed group compare with risk to develop outcome of interest in non-exposed. For this study, ORs represent risk to develop SJS/TEN in people carrying at least one allele of *HLA genotypes* compare with people who do not possess the gene.

5. Diamonds: Summary results from meta-analysis will be presented in this part. The size of the diamond represents the total size of the pooled study. The horizontal corners of the diamond represent the width of the confidence intervals of the result.

6. Summary odds ratio results: Combination result of the individual studies will be reported in this part.

7. % Weight: Percentage of that each included study has a different magnitude influencing the pooled result.

8. Random effects model: The model used to perform the meta-analysis will be showed in this part. There are 2 different approaches to conduct statistical analysis: fixed-effects and random-effects meta-analysis.

1. Fixed-effects model assume that the intervention has the same size of effect across all the studies. Using this model tend to have narrower confidence intervals than random effects models.

2. Random effects models assume that this effect size may vary between trials and produce results with wider confidence intervals.

9. Heterogeneity: Results of heterogeneity testing will be presented in term of the I-squared and Q-statistics tests. Both of these tests represent whether the difference between results of individual studies are due to chance or effect. I-squared test indicates level of difference whereas, Q-statistics test shows statistically significant.

Advantages of systematic reviews and meta-analysis [57, 60, 61]

Major advantage of systematic reviews and meta-analysis is well-defined methods which reducing bias by identifying, appraising and synthesizing all relevant studies. While narrative reviews remain informative, they are prone to bias as authors are freely to select only articles that they believe are important or interesting. Combination of results from two or more separate studies, meta-analysis approach can increased power, improve precision, improve generalizability and consistency of results and answer questions not posed by individual studies. In addition, searching and selection steps in systematic reviews aim to identify all relevant studies that meet the eligibility criteria. Nonetheless, in extracting data steps, important information from all relevant studies will be extracted. Systematic reviews can provide conclusive

summaries from all relevant studies, identified gaps of knowledge of existing studies, and generation of new hypotheses.

Table 1 Comparison between narrative and systematic review

Core	Narrative Review	Systematic Review Study
Feature question	Often broad in scope	Often a focused clinical question
Data sources and search strategy	Specifications of database searched and search strategy are not typically provided	Comprehensive search of many databases as well as the so-called gray literature. Explicit search strategy provided
Selection of articles for study	Not usually specified. If specified, potentially biased	Criterion-based selection, uniformly applied
Article review or appraisal	Variable, depending on who is conducting the review	Rigorous critical appraisal, typically using a data extraction form
Study quality	Usually not assessed. If assessed, may not use formal quality assessment	Some assessment of quality is almost always included as part of the data extraction process.
Synthesis	Often a qualitative summary	Quantitative or qualitative summary
Inferences	Occasionally evidence based	Usually evidence based

Weakness of systematic reviews and meta-analysis

Weakness or limitations of meta-analysis can arise as follow;

1. Quality of the included studies

One problem with meta-analysis is low quality or lack validity of the included studies. As a result, a meta-analyses based on combination of these studies, can produce low quality or lack validity result. These may be characterized as garbage-in-garbage-out.

2. Publication bias

The studies with favorable results are more likely to be published than those with inconclusive results. While many studies were not published and others are published in an abstract form, but not as a full report form. Identification of all relevant studies may be difficult based on publication in less accessible journals (e.g., non-English language).

3. Small sample sizes

An additional limitation of meta-analysis is, in some cases, the included studies having small sample sizes. Studies based on small sample sizes typically have a low statistical power, and a large standard error. As a result, a meta-analyses based on these studies can produce effect sizes that are very heterogeneous, and the findings may lead to erroneous inferences.

CHAPTER III

RESEARCH METHODOLOGY

Identification of studies

A comprehensive and systematic search were performed from the inception of the following databases: PubMed/Medline (U.S. National Library of Medicine, Bethesda, MD, USA), HuGENet (Human Genome Epidemiology Network), and Cochrane library, using the keywords, synonyms and other terms related to *HLA* genotypes and the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) (Table 2). There was no restriction on language or study design. Only human studies are included. Additional studies were retrieved from reference lists of the selected articles.

Table 2 Search terms used for identifying relevant studies.

Drugs	Search terms
Dapsone	"Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigen" OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene
	Dapsone
Methazolamide	"Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigen" OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene
	Methazolamide
Oxcarbazepine	"Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigen" OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene
	Oxcarbazepine

Appraisal and selection of studies

Studies were included for case and control groups if: (1) *HLA* genotypes and the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) induced adverse drug reactions were investigated and (2) All patients in both case and control groups received the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) before the *HLA* genotype screening

Studies were excluded if: (1) a study meets the inclusion criteria but does not provide sufficient information for future analysis and (2) two or more studies shared the same population, a study with a more complete data or a larger sample size was selected for our study.

Data extraction and quality assessment

Important information [i.e., study design, eligibility criteria, definition, and diagnostic criteria for cases and controls, patient demographics, dose and duration of the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) exposure, the HLA genotyping technique and Hardy-Weinberg equilibrium (HWE) information were extracted and systematically tabulated.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the case control and cohort studies. Three quality domains including selection, comparability, and outcome or exposure was taken into consideration, depending on the study design [62].

Data analyses

Systematic review

The previous studies demonstrating the association between *HLA* genotypes and the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) induced adverse drug reactions were characterized and summarized based on the most updated data.

Meta-analysis

Meta-analyses were performed when there are data of the same *HLA* genotypes, types of affecting drugs, and the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) from two or more separate studies.

The overall odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to determine the associations between the presence of *HLA* genotypes and the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) induced ADRs.

Notably, to determine the association from observational study, the results can be calculated in term of relative risk (RR) and odds ratio (OR). RR is the ratio of the incidence rate of the outcome in exposed group compare with the incidence rate of the outcome in non-exposed group. Whereas, OR is the odds that an outcome will occur exposed group, compared to the odds of the outcome occurring in non-exposed group.

In cohort study, RR can be directly calculated. However, in case-control study, the size of either exposed population or non-exposed population cannot be acquired. The result from case control study cannot provide incidence rates of the outcome in exposed or non-exposed individual. Therefore, RR cannot be calculated directly from case-control study. However, RR and OR are closely estimate when the outcome under study is relatively rare disease/outcome. Since case-control studies are generally used to study rare disease/outcome.

For this study, OR is a measure of association between an exposure and an outcome, in this case, *HLA* genotypes and methazolamide-induced cADRs, respectively. OR represents the odds of development of cADRs induced by the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) in subjects carrying the *HLA* genotypes (case), compared with the odds of non-development of cADRs induced by the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) in subjects carrying the *HLA* genotypes (control) [58, 59, 63].

Odds ratio will be calculated using a two-by-two frequency table (shown below).

	Case	**Control**	**Total**
***HLA* genotypes positive**	a	b	a+b
***HLA* genotypes negative**	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$\textbf{Odds Ratio} = (a/b) / (c/d)$$

Where

a = Number of subjects carrying the *HLA* genotypes positive in cases

b = Number of subjects carrying the *HLA* genotypes positive in control

c = Number of subjects who do not possess the *HLA* genotypes in cases

d = Number of subjects who do not possess the *HLA* genotypes in control

When

OR = 1: *HLA* genotypes does not affect odds of drug-induced ADRs

OR > 1: *HLA* genotypes associated with drug-induced ADRs

OR < 1: *HLA* genotypes associated with drug-induced ADRs

All analyses were performed using the DerSimonian and Laird method under a random-effects model [64]. The analyses were also performed separately on the studies using different types of control (e.g., tolerant or general population control), different types of *HLA* genotypes and different types of cADRs.

Notably, a general population control was defined as healthy subjects providing *HLA* genotypes information (i.e. allele frequencies). This information can be retrieved from allele frequencies databased, studies reporting allele frequencies of the genes. Whereas a tolerant control was defined by information of *HLA genotypes* in the control group obtained from subjects who received the drugs of interest (i.e., dapsone, methazolamide and oxcarbazepine) without any history of cADRs.

Statistical heterogeneity were assessed via the Q-statistics and I-squared tests [65]. A p-value of ≤ 0.10 indicates heterogeneity between studies. I-squared values of 25%, 50%, 75% denote a low, moderate, and high of heterogeneity across studies, respectively [66].

If the included studies more than 10 studies in each association, publication bias were evaluated via funnel plot, Begg's test [67], and Egger's test [68]. If the publication bias is identified, the trim-and-fill method was employed to correct for this bias [69].

Subgroup analysis [e.g., study design, ethnicity, diagnostic method, types of control) e.g., tolerant controls or healthy controls (and type of adverse drug reactions) were conducted to explore potential sources of heterogeneity.

All statistical analyses were performed using the R Program (version 3.4.0) (R Foundation for Statistical Computing 2017).

CHAPTER IV

RESULTS AND DISCUSSIONS

This chapter was divided into 3 separate section as follows: 1) Dapsone; 2) Methazolamide, and; 3) Oxcarbazepine.

Section I: Dapsone

Result of dapsone

Search strategy and selection criteria

Our literature search strategy and study selection process are summarized in Figure 10. The initial search of the databases identified 391 articles. After duplicate records were removed, 365 articles were screened on the basis of title, abstract, or both to determine eligibility. Three articles [17, 19, 70] met inclusion criteria. No additional articles were identified in the bibliographies of the included studies.

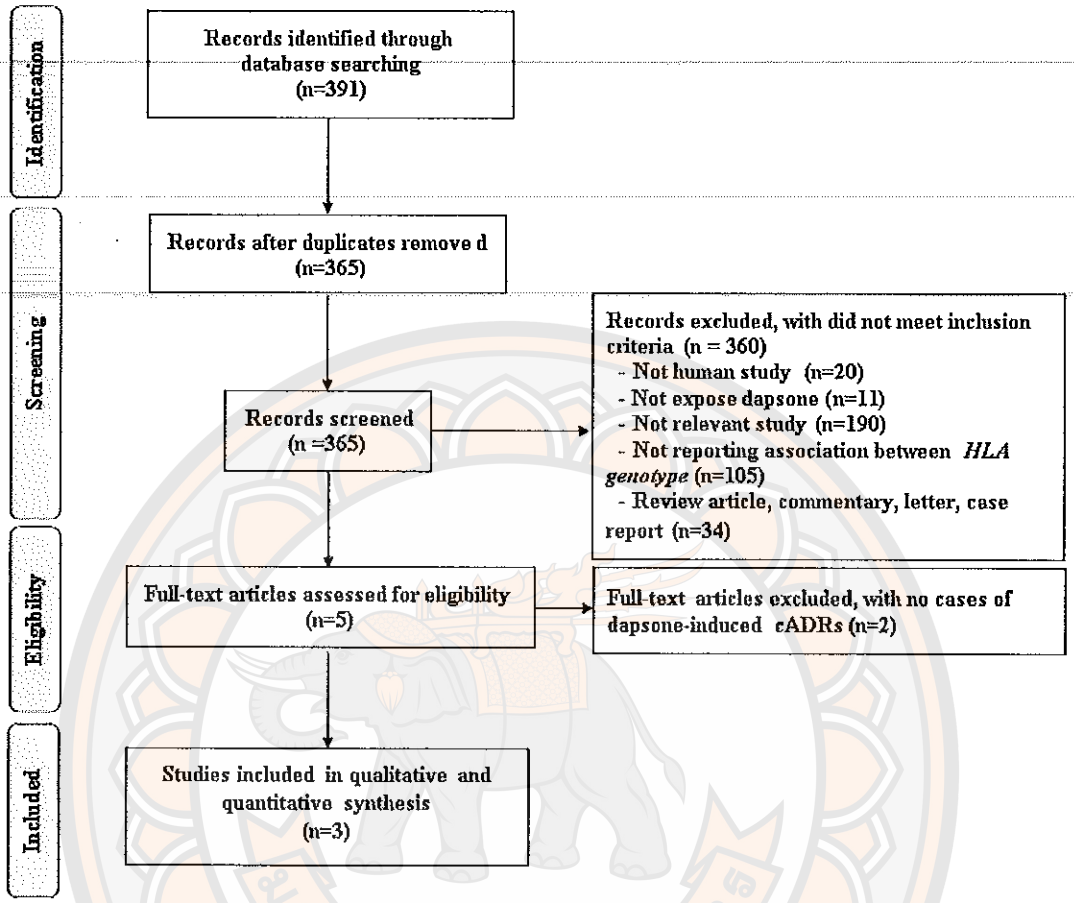

Figure 10 PRISMA flow diagram of *HLA-B*1301* and dapsone-induced cutaneous adverse drug reactions

Study characteristics and quality assessment

Characteristics of the included studies are summarized in Table 3. All of the included studies were case-control studies [17, 19, 70]. One hundred eleven unique case patients with dapsone-induced cADRs [17, 19, 70], 1,165 dapsone-tolerant controls [17, 19, 70], and 3,026 healthy controls [17, 19, 70] were included in our systematic review and meta-analysis. Mean age of included patients was 39.7 years in case patients [17, 19, 70], 32.2 years in dapsone-tolerant control patients [17, 70] , and 39.5 years in healthy controls [17]. Because some of the selected studies in this meta-analysis did not provide individual data points, SDs could not be calculated from the

available information. Male patients made up 64 of 113 cases (56.6%) [17, 19, 70] 2 patients were missing from the meta-analysis; each from the study by Wang, et al. [17] and Zhang, et al. [70]), 817 of 1,144 dapsone-tolerant controls [17, 70] (71.4%), and 53 of 100 healthy controls (53.0%) [17]. The mean dose of dapsone was 94.5 mg/d (range, 2-100 mg/d) [19]. Mean duration of dapsone-induced cADRs was 30.4 days (range, 1-53 days) [17, 70]. All of the included studies were conducted in Asian populations (2 in Chinese populations [17, 70] and 1 in a Thai population [19]). The studies by Wang, et al. [17] and Zhang, et al. [70] investigated the association between *HLA-B*1301* and DHS, whereas Tempark, et al. [19] investigated the association between *HLA-B*1301* and dapsone-induced severe cADRs. Diagnostic criteria for DHS, SJS/TEN, and DRESS for each study are summarized in Table 2. The included studies identified *HLA* genotypes by using polymerase chain reaction sequence-specific primers [17], polymerase chain reaction next-generation sequencing [70], and polymerase chain reaction sequence-specific oligonucleotide primers [19] . In the study by Zhang, et al. [70], reported controls deviated significantly from the Hardy-Weinberg equilibrium ($P < 10^{-8}$). The mean score of quality assessment using the Newcastle-Ottawa scale for case-control studies was 6.3 (range, 5-7) (Table 3).

Table 3 Characteristics of included studies

Author (Year)	Ethnicity	*HLA* genotypes	Type of cADRs (n)	Control (n)	Diagnostic criteria		NOS
					Case	Control	
Wang, et al. (2013) [17]	Chinese (Han Chinese= 53.8%, Non-Han Chinese=46.2%)[a]	*HLA-B*1301, HLA-B*1313, HLA-C*0304*	DHS (20)	Tolerant control (n=102)	Subjects who took dapsone for 8 weeks and developed DHS. DHS was diagnosed using Richardus and Smith's (1989) criteria.	Subjects who took dapsone for more than 8 weeks without any episode of drug eruption and reaction	6
				Healthy control (n=96)		NR	
Zhang, et al. (2013) [70]	Chinese	*HLA-B*1301, HLA-C*0304*	DHS (76)	Tolerant control (n=1034)[b]	Subjects who took dapsone and developed DHS. DHS was diagnosed using Richardus and Smith's (1989) criteria.	Subjects who took dapsone at least 6 months without DHS	7
				Healthy control (n=523 Shandong, 470 Yunnan, 951 Guangdong)		NR	
Tempark, et al. (2017) [19]	Thai	*HLA-B*1301, HLA-B*1502, HLA-B*4001, HLA-B*4601, HLA-B*5801*	SJS, TEN, and DRESS (15)	Tolerant control (n=29)	SJS, TEN, and DRESS were diagnosed using RegiSCAR criteria. SJS and TEN were defined as skin detachment less than 10% and 30% of body surface area, respectively. DRESS was defined by the triad of skin eruption, hematological involvement, and internal organ involvements according to the RegiSCAR Diagnosis Score.	Subjects who took dapsone dapsone more than 6 months without evidence of cADRs	6
				Healthy control (n=986)		NR	

Note: cADRs = cutaneous adverse reactions; DHS = dapsone-induced hypersensitivity; DRESS = drug rash with eosinophilia and systemic symptoms; NOS = The Newcastle-Ottawa scale; NR = not report; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

[a] Average number from case, tolerant control, and healthy control [b] Number of subjects in the analysis

Statistical analysis

Analysis using dapsone-tolerant control studies

The associations between *HLA-B*1301* and dapsone-induced cADRs are summarized in Table 3. One hundred eleven patients had dapsone-induced cADRs and 1,165 were dapsone tolerant. In these studies, 95 cases and 157 controls carried at least 1 *HLA-B*1301* allele. We found an association between *HLA-B*1301* and dapsone-induced cADRs (summary OR, 43.0; 95% CI, 24.0-77.2). There was no heterogeneity (I^2=0%, p= 0.38) (Table 4 and Figure 11).

In a subgroup analysis by types of cADR, ORs were 51.7 (95% CI, 16.9-158.5; I^2= 46%; p=0.17) in the DHS group; 54.0 (95% CI, 8.0-366.2) in the dapsone-induced severe cADRs (SJS/TEN plus DRESS) group; 40.5 (95% CI, 2.8-591.0) in the dapsone-induced SJS/TEN group; and 60.8 (95% CI, 7.4-496.0) in the dapsone-induced DRESS group (Table 4).

Analysis using healthy control studies

There were 100 patients with dapsone-induced cADRs and 3,026 healthy controls. In these studies, 95 cases and 39 controls carried at least 1 *HLA-B*1301* allele. Statistically significant associations between *HLA-B*1301* and dapsone-induced cADRs were identified (Table 4).

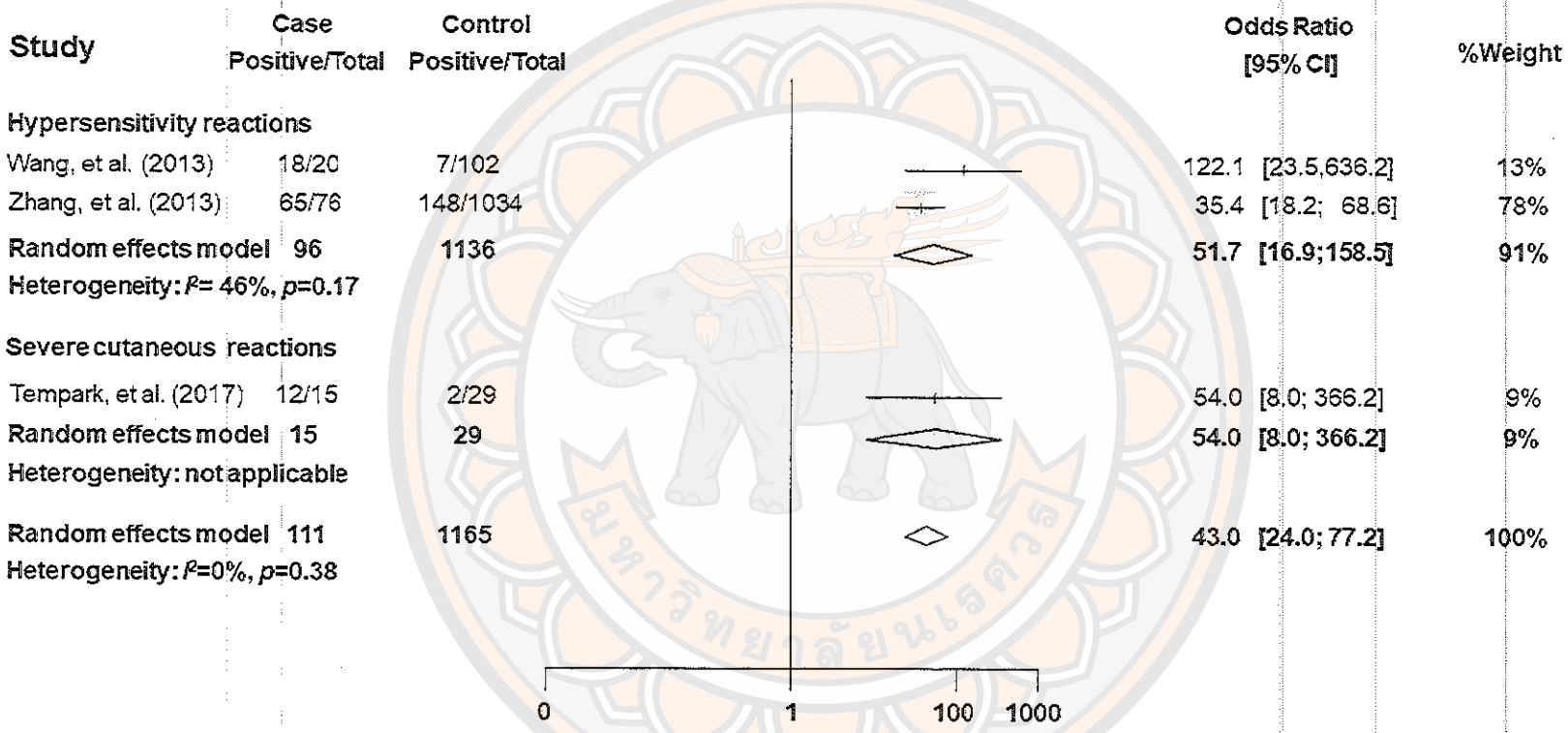

Figure 11 Forest plots of the associations between *HLA-B*1301* and dapsone-induced cutaneous adverse drug reactions using dapsone tolerant control studies

Table 4 Calculated odds ratios of the included studies and summary odds ratios categorized by types of control and cutaneous adverse drug reactions

Author (Year)	Type of cADRs	Ethnicity	*HLA-B*1301* Positive/Total		Odds Ratio (95%CI)
			Case	Control	
Dapsone-tolerant Control Studies					
Wang, et al. (2013) [19]	DHS	Chinese	18/20	7/102	1221.1 (23.5-636.2)
Zhang, et al. (2013) [70]	DHS	Chinese	65/76	148/1034	35.4 (18.2-68.6)
Sub-total (I^2 =46%, p=0.17)					**51.7 (16.9-158.5)**
Tempark, et al. (2017) [19]	SJS/TEN	Thai	3/4	2/29	40.5 (2.8-591.0)
	DRESS	Thai	9/11		60.8 (7.4-496.2)
Sub-total (I^2 =NA, p=NA)					**54.0 (8.0-366.2)**
Summary odds ratio (I^2=0%, p=0.38)					**43.0 (24.0-77.2)**
Healthy Control Studies					
Wang, et al. (2013) [19]	DHS	Chinese	18/20	11/96	69.6 (14.2-341.1)
Zhang, et al. (2013) [70]	DHS	Chinese (Shandong)	65/76	35/523	82.4 (39.9-170.2)
		Chinese (Yunnan)		64/470	37.5 (18.8-74.8)
		Chinese (Yunnan)		157/951	29.9 (15.4-57.9)
Tempark, et al. (2017) [19]	SJS/TEN	Thai	3/4	131/986	19.6 (6.3-134.4)
	DRESS	Thai	9/11		29.4 (6.3-137.4)

Note: 95%CI = 95%confidence intervals; cADRs =cutaneous adverse reactions; DHS = dapsone-induced hypersensitivity; DRESS =drug rash with eosinophilia and systemic symptoms; HLA =human leukocyte antigen; NA =not applicable; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

Discussions of the dapsone section

To our knowledge, this is the first systematic review and meta-analysis to identify the associations between *HLA-B*1301* and dapsone-induced cADRs. An association was found between the *HLA-B*1301* and dapsone-induced cADRs (summary OR, 43.0; 95% CI, 24.0-77.2) (Figure 11). This statistically significant association was similar to the results of the subgroup analyses in the DHS, dapsone-induced severe cADRs (SJS/TEN plus DRESS), dapsone-induced SJS/TEN, and dapsone-induced DRESS groups (Table 3). In addition, the association between *HLA-B*1301* and dapsone-induced cADRs was found in healthy controls. In the healthy control group, there were duplicate cases in Zhang, et al. [17] Therefore, summary ORs could not be calculated and this study was not included in the meta-analysis. However, the observed ORs as shown in Table 4 are still relatively high.

Allele frequency of *HLA-B*1301* (*f*) was 0 to 0.019 in European patients, 0.021 in Korean patients, and 0 to 0.015 in Japanese patients. This allele is more prevalent among Chinese (f = 0.009-0.211) and Southeast Asian (f = 0.091-0.021) populations. Prevalence of *HLA-B*1301* is higher in Papua New Guinean (f = 0.283-0.132) and Australian Aboriginal (f = 0.132-0.270) populations [71]. Nonetheless, outcomes of the dapsone-induced cADRs among persons of other races/ethnicities carrying *HLA-B*1301* might be different from those in Chinese and Southeast Asian populations.

Our study demonstrated associations between *HLA-B*1301* and dapsone-induced DHS in 2 Chinese populations [17, 70] and between *HLA-B*1301* and dapsone induced severe cADRs (SJS/TEN plus DRESS) in 1 Thai population [19]. To identify any association between *HLA-B*1301* and dapsone-induced cADRs in other populations from other geographic areas, future studies are needed.

Recently, a mechanism by which *HLA-B*1301* causes DHS was proposed by Watanabe, et al. [72] Dapsone specifically binds to *HLA-B*1301* at the residue Ile95, a proposed binding site called "pocket F." This specific binding between dapsone and

*HLA-B*1301* alters the structure of the antigen-recognition site of HLA B*1301. As a result, the structurally altered protein can recognize its ligands and this leads to the dapsone-induced cADRs.

Section II: Methazolamide

Result of methazolamide

Search strategy and selection criteria

Our literature search strategy and study selection process are depicted in Figure 12. The initial search from the databases identified 92 article. After duplicate records were removed, 87 articles were first screened on the basis of title and/ or abstract to determine the eligibility. Two articles from Korean and Han Chinese population met the inclusion criteria. [25, 27] No additional articles were identified in the bibliographies of the included studies.

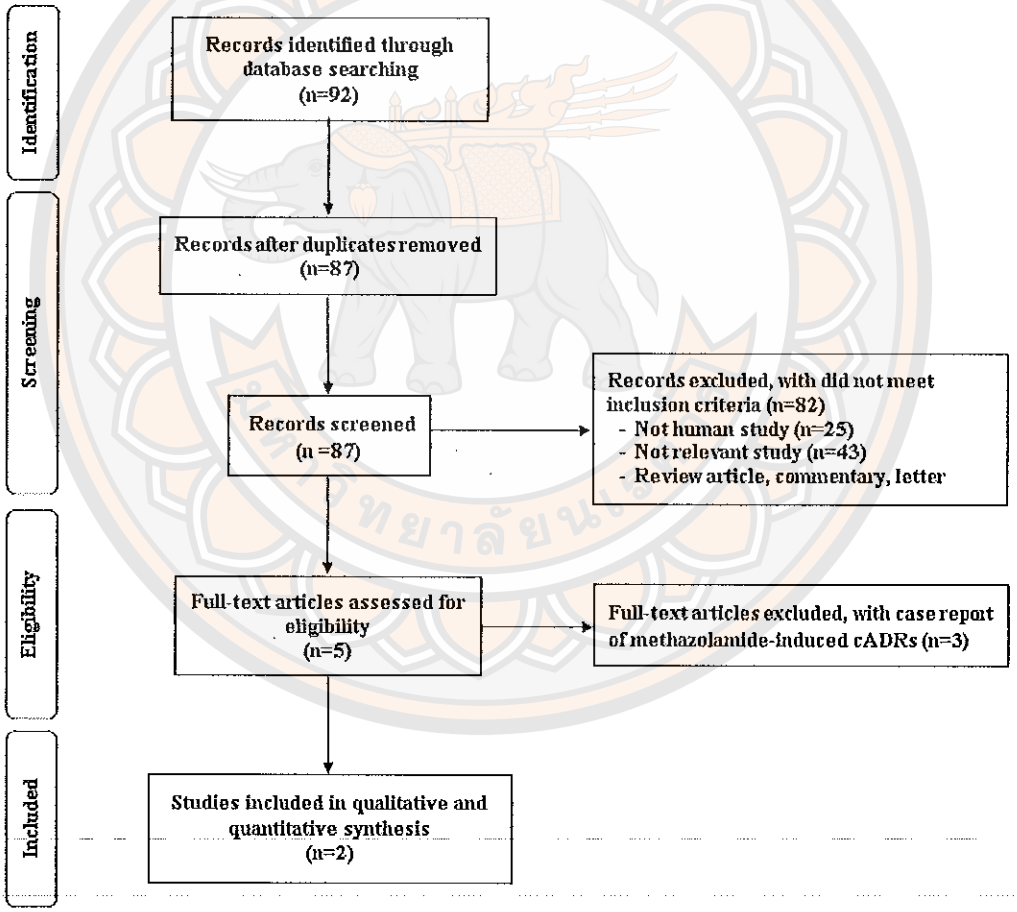

Figure 12 PRISMA flow diagram of *HLA* genotypes and methazolamide-induced cutaneous adverse drug reactions

Study characteristics and quality assessment

Characteristics of the included studies are summarized in Table 5. In total of 13 patients with methazolamide-induced SJS/TEN [25, 27], 30 methazolamide-tolerant [27] and 768 general population controls [25, 27] were included in our systematic review and meta-analysis. Both of the included studies were case-control studies examining associations between *HLA* genotypes and methazolamide-induced SJS/TEN [25, 27]. TEN was developed in 10 out of 13 (76.9%) patients with methazolamide-induced SJS/TEN group [25, 27]. Mean ages of the patients were 46 years [25, 27] and 57.6 years [27] in cases and in methazolamide-tolerant controls, respectively. Male subjects made up of 61.5% (8 of 13) of cases [25, 27] and 36.7% (11 of 30) methazolamide-tolerant controls [27]. The range dose of methazolamide was 50-150 mg/day [25, 27]. Mean duration of methazolamide-induced SJS/TEN was 16.5 days (rang 1-58 days) [25, 27]. Both of the included studies conducted in Asian population (1 study in Korean population [25] and another study in Han Chinese population [27]). All of the included studies investigated the associations between *HLA-B*5901*, *HLA-Cw*0102*, the haplotype and methazolamide-induced SJS/TEN [25, 27]. Nonetheless, Kim, et al. [25] also investigated the associations between *HLA-A*2402* and methazolamide-induced SJS/TEN. Diagnostic criteria for SJS/TEN of the two studies is summarized in Table 4. Yang, et al. [27] used polymerase chain reaction sequencing of specific oligonucleotide (PCR-SSO) to identify *HLA* genotypes whereas, Kim, et al. [25] used a direct DNA sequence analysis technique. HWE information were not reported in neither one of the included studies [25, 27]. A mean value of the quality assessment using the NOS of case-control studies was 6.5 (range 6-7) (Table 5).

Table 5 Characteristics of the included studies

Author (Year)	Ethnicity	*HLA* genotypes	Type of cADRs (n)	Control (n)	Diagnostic criteria		NOS
					Case	Control	
Kim SH, et al. (2010) [25]	Korean	*HLA-A*2402, HLA-B*5901, HLA-Cw*0102*	SJS/TEN (n=5)	General population (n=485)	SJS and TEN were defined as mucocutaneous disorders characterized by extensive erythema, blistering, epidermal detachment, erosions, exanthema and high fever. The diagnostic criteria of SJS/TEN were based on the clinical morphology described by Roujeau (SJS: skin detachment of <10% of total body surface area; SJS/TEN overlap: skin detachment of 10-30%; TEN: skin detachment of >30%). All subjects were thoroughly reviewed by allergy specialists and dermatologists for accurate phenotype diagnosis and confirmation of methazolamide as a causative agent.	*HLA* genotypes information obtained from Lee et al.	6

Table 5 (cont.)

Author (Year)	Ethnicity	*HLA* genotypes	Type of cADRs (n)	Control (n)	Diagnostic criteria		NOS
					Case	Control	
Yang F, et al. (2016) [27]	Han Chinese	*HLA-B*5901, HLA-Cw*0102*	SJS/TEN (n=8)	General population (n=283)	Subjects who developed SJS or TEN symptoms within the first 2 months after methazolamide treatment and the symptoms resolved after withdrawal of the drug. SJS, overlap SJS/TEN and TEN were defined as epidermal detachment of skin detachment less th 33 %, 10-30%, and >30% of tota surface area, respectively. Diagnoses of SJS and ere confirmed by two independent dermatologists who examined photographs, pathological slides and medical records.	*HLA* genotypes information of healthy southern Han Chinese subjects obtained from the human major histocompatibility complex database.	7
				Methazolamide-tolerant control (n=30)		Subjects who did not develop any cutaneous manifestations at least 3 months after methazolamide treatment	

Note: cADRs = cutaneous adverse reactions; HLA = human leukocyte antigen; NOS = The Newcastle-Ottawa scale; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

Statistical analysis

Associations between *HLA-B*5901* and methazolamide-induced SJS/TEN

We found strong associations between *HLA-B*5901* and methazolamide-induced SJS/TEN in both methazolamide-tolerant and general population controls. The numbers of patients carrying with at least one allele of *HLA-B*5901* were 7 out of 8 in cases and none out of 30 in methazolamide-tolerant controls [27]. In methazolamide-tolerant controls group, the overall OR was 305.0 (95%CI=11.3-8,259.4) (Figure 11A and Table 5). The numbers of patients carrying with at least one allele of *HLA-B*5901* were 12 out of 13 in cases and 21 out of 768 in general population controls [25, 27]. In general population controls group, the overall OR was 715.3 (95%CI=83.1-6,158.5). There was no heterogeneity (I^2=9.3%, p=0.29) (Figure 13A and Table 6).

Associations between *HLA-Cw*0102* and methazolamide-induced SJS/TEN

Associations between *HLA-Cw*0102* and methazolamide-induced SJS/TEN were found in both methazolamide-tolerant and general population controls. The numbers of patients carrying with at least one allele of *HLA-Cw*0102* were 7 out of 8 in cases and 11 of 30 in methazolamide-tolerant controls [27]. In methazolamide-tolerant controls group, the overall OR was 12.1 (95%CI=1.3-111.7) (Figure 11B and Table 5). The numbers of patients carrying with at least one allele of *HLA-Cw*0102* were 12 out of 13 in cases and 108 out of 768 in general population controls [25, 27]. In general population controls group, the overall OR was 17.5 (95%CI=3.2-96.6). There was no heterogeneity (I^2=0.0%, p=0.85) (Figure 13B and Table 6).

Associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN

Strong associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were also found in both methazolamide-tolerant and general population controls. The numbers of patients carrying this haplotype were 7 out of 8 in cases and none out of 30 in methazolamide-tolerant controls [27]. In methazolamide-tolerant controls group, the overall OR was 305.0 (95%CI=11.3-8,259.4) (Figure 13C and Table 6). The numbers of patients carrying this haplotype

were 12 out of 13 in cases and 21 out of 768 general population controls [25, 27]. In general population controls group, the overall OR was 715.3 (95%CI=83.1-6,158.5). There was no heterogeneity (I^2=9.3%, p=0.29) (Figure 13C and Table 6).

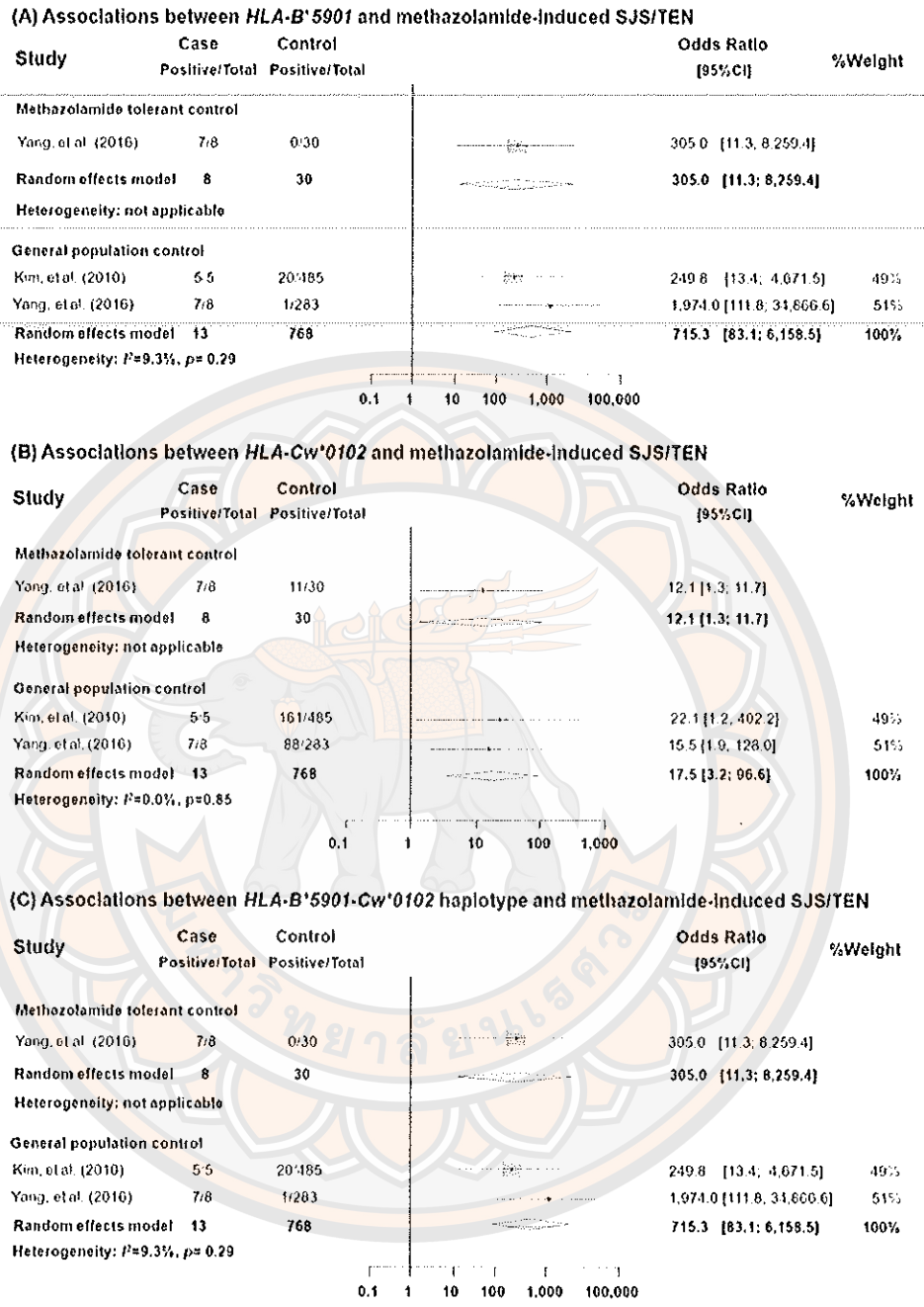

Figure 13 Forest plots of the associations between *HLA-B*5901* and methazolamide-induced SJS/TEN (A), the associations between *HLA-Cw*0102* and methazolamide-induced SJS/TEN (B), and, the associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN (C)

Table 6 Calculated odds ratios of the included studies and summary odds ratios categorized by types of control and cutaneous adverse drug reactions

Author (Year)	Type of cADRs	Ethnicity	*HLA* genotypes Positive/Total		Odds Ratio (95%CI)
			Case	Control	
HLA-B*5901					
Methazolamide tolerant control					
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	0/30	305.0 (11.3-8,259.4)
General population					
Kim SH, et al. (2010) [25]	SJS/TEN	Korean	5/5	20/485	249.8 (13.4-4,671.5)
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	1/283	1,974.0 (111.8-34,866.6)
Summary odds ratio (I^2=9.3%, p=0.29)					**715.3 (83.1-6,158.5)**
HLA-Cw*0102					
Methazolamide tolerant control					
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	11/30	12.1 (1.3-111.7)
General population					
Kim SH, et al. (2010) [25]	SJS/TEN	Korean	5/5	20/485	22.1 (1.2-402.2)
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	88/283	15.5 (1.9-128.0)
Summary odds ratio (I^2=0%, p=0.85)					17.5 (3.2-96.6)
HLA-B*5901, HLA-Cw*0102					
Methazolamide tolerant control					
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	0/30	305.0 (11.3-8,259.4)
General population					
Kim SH, et al. (2010) [25]	SJS/TEN	Korean	5/5	20/485	249.8 (13.4-4,671.5)
Yang F, et al. (2016) [27]	SJS/TEN	Han Chinese	7/8	1/283	1,974.0 (111.8-34,866.6)
Summary odds ratio (I^2=0%, p=0.29)					**715.3 (83.1-6,158.5)**

Note: 95%CI = 95%confidence intervals; cADRs = cutaneous adverse reactions; HLA = human leukocyte antigen; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis

Discussions of the methazolamide

To our knowledge, this is the first systematic review and meta-analysis study to identify the associations between *HLA-B*5901* and methazolamide-induced SJS/TEN. Strong associations between *HLA-B*5901* and methazolamide-induced SJS/TEN with summary ORs of 305.0 (95%CI=11.3-8,259.4) and 715.3 (95%CI=83.1-6,158.5) in methazolamide-tolerant and general population controls, respectively. (Figure 13A, and Table 6). These statistically significant associations were as high as when compared to the results of the associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN in both methazolamide-tolerant and general population controls (Figure 11C, and Table 5). In addition, the association between the *HLA-Cw*0102* and methazolamide-induced SJS/TEN was also identified in methazolamide-tolerant and general population controls. Summary ORs were 12.1 (95%CI=1.3-111.7) and 17.5 (95%CI=3.2-96.6) in methazolamide-tolerant and general population controls, respectively. (Figure 13B, and Table 6).

Allele frequency of *HLA-B*5901* (*f*) in Japanese, Korean and Han-Chinese were 0.0090-0.0204, 0.0185-0.0204 and 0-0.0010, respectively. *HLA-B*5901-Cw*0102* haplotype is commonly detected in Japanese and Korean population. *HLA-B*5901-Cw*0102* haplotype frequency in general Japanese population were 1.60% whereas, *HLA-A*2402-B*5901-Cw*0102* were 1.70% in general Korean population [71].

In our study, the associations between *HLA-B*5901, HLA-Cw*0102, HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN in Korean and Han-Chinese population were demonstrated. However, The first case report of methazolamide-induced SJS were reported in two Japanese-American descents [47]. Several case reports of methazolamide-induced SJS/TEN in patients who carried *HLA-B*59* and *HLA-B*5901* were reported in Japanese, Korean and Han-Chinese population [21, 22, 23, 24]. Interestingly, carbonic anhydrase inhibitor drugs (i.e., acetazolamide, brinzolamide and dorzolamide) -induced SJS/TEN were also reported in Japanese, Korean and Han-Chinese population [49, 73, 74, 75]. However, HLA genotyping was not investigated in these studies. Since all of the drugs in this class harbor a sulfone group in their chemical structures, like sulfonamides, it is possible

that other drugs in this group may be able to cause cADRs including SJS/TEN. Thus, more studies investigating associations between *HLA* genotypes and carbonic anhydrase inhibitor drugs-induced cADRs are needed. Since the risk of cADRs of the carbonic anhydrase inhibitors is relatively high, particularly among Asian populations, the drugs should be used with cautions and patients should be informed about these adverse drug reactions prior to the start of their drug treatment.

Section III: Oxcarbazepine

Result of oxcarbazepine

Search strategy and selection criteria

Searching results are depicted in Figure 14. In brief, 91 articles were identified, which was whittled down to 6 studies [29, 30, 76, 77, 78, 79] that met our criteria. These comprised 229 patients with oxcarbazepine-induced cADRs, 251 oxcarbazepine-tolerant patients, and 2,358 participants from general populations [29, 30, 77, 78, 79, 80]. Five studies were case-controlled [29, 77, 78, 79, 80] which formed our systematic review and meta-analysis, and one was a prospective cohort [30] (Table 5).

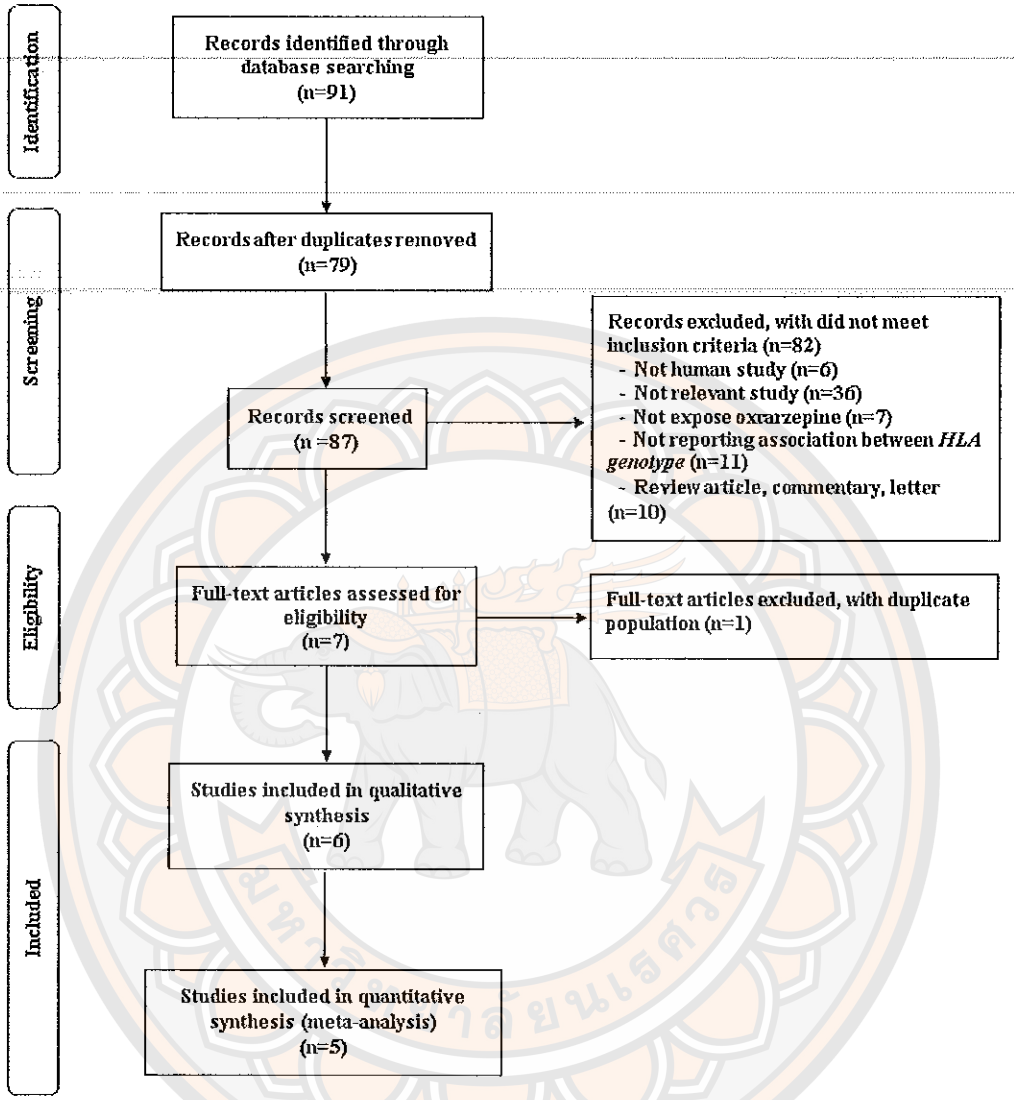

Figure 14 PRISMA flow diagram of *HLA* genotypes and oxcarbazepine-induced cutaneous adverse drug reactions

Study characteristics and quality assessment

Characteristics of the included studies are summarized in Table 7 and 8. Mean ages of included patients were 26.7 years in cases [29, 30, 77, 78, 79, 80] and 34.0 years in controls [78]; males made up 44.3% of cases [29, 30, 77, 78, 79, 80] and 8.9% (11 of 123) of controls [78]. Age and gender data were not reported where controls were from the general population. The mean dose of oxcarbazepine was 315.4 mg/day (range 75-600 mg/day) [29, 30, 77, 78]. The mean delay in appearance of oxcarbazepine-induced cADRs after initiating treatment was 13.9 days (rang 1-53 days) [29, 30, 77, 78]. The included studies identified *HLA* genotypes using polymerase chain reaction (PCR) as a sequence-based typing technique, PCR sequence specific oligonucleotide primers and PCR sequence specific primers. No study reported sample-size calculations before recruiting patients, nor HWE information. A mean quality assessment using NOS for case control studies was 5.8 (range 5-6), whereas NOS scale of the cohort study was 9 (Table 7).

Table 7 Summary of studies investigating the association between *HLA* genotypes and oxcarbazepine-induced cutaneous adverse drug reactions

Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							HLA-A genotypes	*HLA-B* genotypes	*HLA-C* genotypes	
Hu et al, 2011 [29]	Sichuan, China	Han Chinese	Case control	MP rash	9	OXC-tolerant: 9 General population: 72	ND	*HLA-B*1502*	ND	ND
He et al, 2012 [30]	Guangzhou, China	Han Chinese	Prospective cohort	MP rash	14	OXC-tolerant: 35 General population: 264 (southern Han Chinese population), 569 (Hong Kong Chinese population), 106 (Guangzhou Han Chinese population)	ND	*HLA-B*1302* *HLA-B*1501* *HLA-B*1502* *HLA-B*1519* *HLA-B*1527* *HLA-B*2704* *HLA-B*2709* *HLA-B*3905* *HLA-B*4001* *HLA-B*4601* *HLA-B*4804* *HLA-B*4901* *HLA-B*5101* *HLA-B*5401* *HLA-B*5604*	ND	ND

Table 7 (cont.)

Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							HLA-A genotypes	*HLA-B* genotypes	*HLA-C* genotypes	
Lv et al, 2014 [78]	Jilin, China	Han Chinese	Case control	MP rash	14	OXC-tolerant: 28 General population:618 (Beijing Shijiazhuang Tianjin Han population), 105 (North Han Chinese population)	ND	*HLA-B*0705* *HLA-B*1301* *HLA-B*1302* *HLA-B*1301* *HLA-B*1501* *HLA-B*1502* *HLA-B*1511* *HLA-B*1513* *HLA-B*1527* *HLA-B*1542* *HLA-B*1558* *HLA-B*2705* *HLA-B*3508* *HLA-B*3531* *HLA-B*3710* *HLA-B*3801* *HLA-B*3802*	ND	ND

Table 7 (cont.)

Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							HLA-A genotypes	*HLA-B* genotypes	*HLA-C* genotypes	
Lv et al, 2014 [78]	Jilin, China	Han Chinese	Case control	MP rash	14	OXC-tolerant: 28 General population:618 (Beijing Shijiazhuang Tianjin Han population), 105 (North Han Chinese population)	ND	*HLA-B*3901* *HLA-B*4001* *HLA-B*4006* *HLA-B*4402* *HLA-B*4403* *HLA-B*4601* *HLA-B*4701* *HLA-B*4801* *HLA-B*4804* *HLA-B*5101* *HLA-B*5102* *HLA-B*5201* *HLA-B*5301* *HLA-B*5501* *HLA-B*5502* *HLA-B*5601* *HLA-B*5604* *HLA-B*5801*	ND	ND

Table 7 (cont.)

Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							HLA-A genotypes	*HLA-B* genotypes	*HLA-C* genotypes	
Sun et al, 2014 [77]	Wuhan, China	Han Chinese	Case control	MP rash	1	OXC-tolerant: 8 General population: 38	ND	*HLA-B*1502*	ND	ND
				SJS	2	OXC-tolerant: 8 General population: 38				
Moon et al, 2016 [80]	Korea	Korean	Case control	MP rash	40	OXC-tolerant: 70	*HLA-A*3101* *HLA-A*3201*	*HLA-B*1501* *HLA-B*1502* *HLA-B*1511* *HLA-B*4002*	ND	*HLA-DQB1*0501* *HLA-DQB1*0503* *HLA-DRB1*0403* *HLA-DRB1*0406* *HLA-DRB1*1405*

Table 7 (cont.)

Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							HLA-A genotypes	*HLA-B* genotypes	*HLA-C* genotypes	
Chen et al, 2017 [79]	Taiwan	Han Chinese	Case control	MP rash	21	General population: 101	*HLA-A*3101*	*HLA-B*1502*	ND	ND
				SJS	17					
				DRESS	6					
				BFDE	101					
	Thailand	Thai		MP rash	1	OXC-tolerant: 99				
				SJS	3					

Note: BFDE= bullous fixed drug eruption; cADRs = cutaneous adverse drug reactions; DRESS = drug rash with eosinophilia and systemic symptoms; MP rash = maculopapular rash; ND = Not determine; OXC = oxcarbazepine; SJS = Stevens-Johnson syndrom

Table 8 Summary of cutaneous adverse drug reactions definition and diagnostic criteria of the selected studies

Author (Year)	Country	Ethnicity	Type of cADRs	Definition of cADRs	Diagnostic criteria		cADRs evaluation	NOS
					Case	Control		
Hu et al, 2011 [29]	Sichuan, China	Han Chinese	MP rash	MP rash was characterized by cutaneous itchy and erythematous macules and papules.	Subjects who had MP rash after administration of antiepileptic drugs, and spontaneously resolved within 1-2 weeks after withdrawing the causative drugs	General population: Healthy control OXC-tolerant: Subjects who had administered OXC more than 3 months without any cADRs	NR	6
He et al, 2012 [30]	Guangzhou, China	Han Chinese	MP rash	MP rash was characterized by erythematous exanthema without blistering or postulation.	Subjects who had initial symptoms of cADRs within the first 8 weeks of OXC administration	General population: Using the *HLA-B allele* frequency reported in the Allele Frequency Net Database and Trachtenberg et al., 2007 OXC-tolerant: Subjects who had administered OXC more than 3 months without any cADRs	Dermatologist	9

Table 8 (cont.)

Author (Year)	Country	Ethnicity	Type of cADRs	Definition of cADRs	Diagnostic criteria		cADRs evaluation	NOS
					Case	Control		
Lv et al, 2014 [78]	Jilin, China	Han Chinese	MP rash	MP rash was defined as erythematous exanthema without blistering or postulation.	NR	General population: Using the *HLA-B allele* frequency reported in the Allele Frequency Net Database. OXC-tolerant: Subjects who had administered OXC more than 3 months without any cADRs	NR	6
Sun et al, 2014 [77]	Wuhan, China	Han Chinese	MP rash	NR	Subjects who had cADRs within the first 8 weeks of exposure with improvement after drug withdrawal	General population: Healthy Han Chinese children	NR	6
			SJS	SJS was defined as skin detachment of 10% of total body-surface area.		OXC-tolerant: Subjects who had been on OXC for more than 2 months and no cADRs		
Moon et al, 2016 [80]	Korea	Korean	MP rash	NR	Patients who experienced OXC-induced MP rash	General population: Using the *HLA-B allele* frequency reported Lee et al, 2005 OXC-tolerant: Patients who tolerant of OXC	NR	5

Table 8 (cont.)

Author (Year)	Country	Ethnicity	Type of cADRs	Definition of cADRs	Diagnostic criteria		cADRs evaluation	NOS
					Case	Control		
Chen et al, 2017 [79]	Taiwan	Han Chinese	MP rash	MP rash was defined as self-limited diffuse erythematous macules and papules without systemic involvement.	cADRs were determined by the ALDEN algorithm of drug causality assessment and the Naranjo algorithm. Only patients with probable or definite cause of OXC (ALDEN score ≥4 or Naranjo algorithm ≥ 5) were recruited.	General population: NR	At least 2 dermatologists	6
	Thailand	Thai	SJS	SJS was characterized by a rapidly developing blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment less than 10% body surface area skin detachment.		OXC-tolerant: Patients who are tolerant of OXC		
			DRESS	DRESS was characterized by using the criteria and scoring system of the RegiSCAR group include cutaneous involvement with typical skin eruptions (e.g., exfoliative dermatitis, generalized maculopapular exanthema), fever, atypical lymphocytosis, eosinophilia, lymphadenopathy, systemic involvement (e.g., liver, kidney, and lung), time of resolution, and the evaluation of other potential causes.				

Table 8 (cont.)

Author (Year)	Country	Ethnicity	Type of cADRs	Definition of cADRs	Diagnostic criteria		cADRs evaluation	NOS
					Case	Control		
Chen et al, 2017 [79]	Thailand	Thai	BFDE	BFDE was characterized by recurrent with dusky red or heavy pigmented eruptions with blisters mostly on the same sites with re-exposure to the causative agents.	cADRs were determined by the ALDEN algorithm of drug causality assessment and the Naranjo algorithm. Only patients with probable or definite cause of OXC (ALDEN score ≥4 or Naranjo algorithm ≥ 5) were recruited.	OXC-tolerant: Patients who are tolerant of OXC	At least 2 dermatologists	6

Note: ALDEN = Algorithm of drug causality for epidermal necrolysis; BFDE = bullous fixed drug eruption; cADRs = cutaneous adverse drug reactions; DRESS = drug rash with eosinophilia and systemic symptoms; HLA = human leukocyte antigen; MP rash = maculopapular rash; NA = Not applicable; NOS = The Newcastle-Ottawa scale; NR = Not report; OXC = oxcarbazepine; SJS = Stevens-Johnson syndrome

Statistical analysis

MHC class I and oxcarbazepine-induced cADRs

***HLA-A* genotypes**

The associations between *HLA-A* genotypes and oxcarbazepine-induced cADRs of the included studies are summarized in Table 9. Two studies investigated associations between *HLA-A* genotypes (i.e., *HLA-A*3101* and *HLA-A*3201*) and several types of oxcarbazepine-induced cADRs (i.e., maculopapular rash, SJS, DRESS and BFDE) [80]. However, there were only sufficient data to assess the association between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash that could be meta-analyzed. Associations between *HLA-A*3201* and oxcarbazepine-induced maculopapular rash were determined by Moon, et al. [79, 80] in general population control and oxcarbazepine-tolerant groups. An association between *HLA-A*3201* and oxcarbazepine-induced maculopapular rash was found in general population controls (overall OR=8.46, 95%CI=1.37-52.2) (Table 9). Moon, et al. [80] and Chen, et al. [79] found 8 out of 53 *HLA-A*3101* carriers in their cases general population controls, the numbers of and controls were 5 out of 579. We found an association between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash in the general population controls (overall OR=29.2, 95%CI=6.70-128; I^2=0.0%, p=0.45) (Figure 15). In oxcarbazepine-tolerant controls, the number of *HLAA* 3101* carriers in cases was 6 out of 35 and 15 out of 156 for controls. However, there was no statistically significant association between *HLA-A* 3101* and oxcarbazepine-induced maculopapular rash in oxcarbazepine-tolerant group (Figure 15).

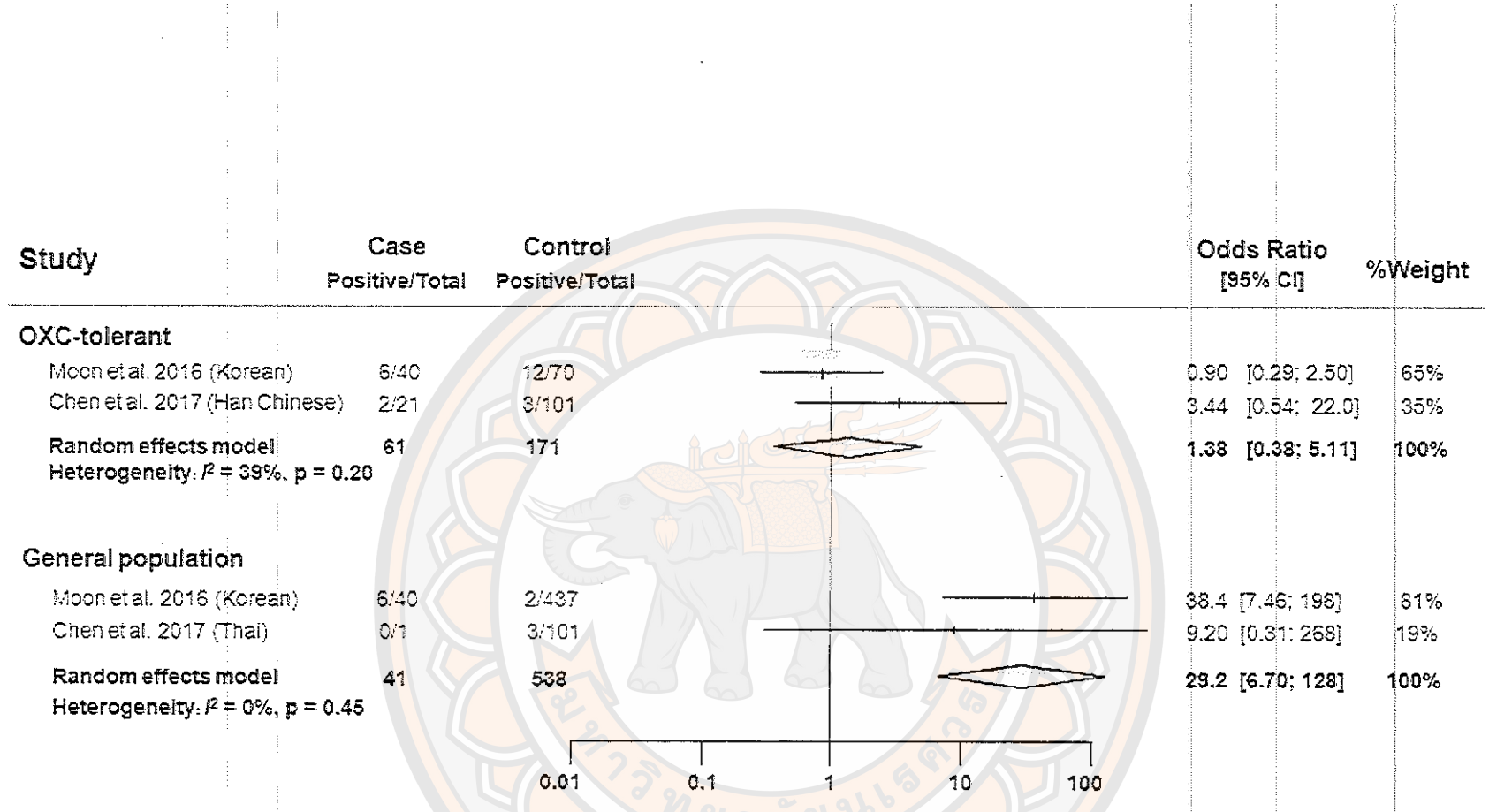

Figure 15 Forest plot of the associations between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash

***HLA-B* genotypes**

The associations between *HLA-B* genotypes and oxcarbazepine-induced cADRs of the included studies are summarized in Table 9. Among all of the included studies [29, 30, 77, 78, 79, 80], 42 different *HLA-B* genotypes and several types of oxcarbazepine-induced cADRs are investigated. Associations between *HLA-B*1501*, *HLA-B*1502*, and *HLA-B*1511* and oxcarbazepine-induced cADRs could be included into our further meta-analyses. Associations between *HLA-B*1502* and oxcarbazepine-induced cADRs were identified. All included studies investigated associations between *HLA-B*1502* and different types of oxcarbazepine-induced cADRs [29, 30, 77, 78, 79, 80]. Two studies investigated associations between *HLA-B*1502* and oxcarbazepine-induced SJS in general population controls and oxcarbazepine-tolerant group [77, 79]. In the general population groups, there were 4 *HLA-B*1502* carriers out of 5 cases and 14 out of 137 for controls. The overall OR was 30.2 (95%CI=3.45-264; I^2=0.0%, p=0.80) (Figure 16 and Table 9). In oxcarbazepine-tolerant controls, there were 13 *HLA-B*1502* carriers out of 19 cases and 8 out of 109 for controls. The overall OR was 26.4 (95%CI=7.98-87.6; I^2=0.0%, p=0.64) (Figure 16 and Table 7).

All of the included studies investigated associations between *HLA-B*1502* and oxcarbazepine-induced maculopapular rash [29, 30, 77, 78, 79, 80]. However, only case control studies were meta-analyzed. In the case control studies, the incidence of *HLA-B*1502* carriers in cases, general population control, and oxcarbazepine-tolerant groups were 6 out of 67, 51 out of 1,930, and 15 out of 216 respectively [29, 30, 77, 78, 79, 80]. In general population controls, the overall OR was 5.67 (95%CI=2.03-15.9; I^2=0.0%, p=0.76) (Figure 17 and Table 9).

In addition, we combined numbers of oxcarbazepine-induced maculopapular rash and oxcarbazepine-induced SJS events in to further investigate their associations between *HLA-B*1502* and oxcarbazepine-induced maculopapular rash and SJS. In general population controls only, *HLA-B*1502* was associated with oxcarbazepine-induced maculopapular rash and SJS; overall OR was 7.15 (95%CI=2.64-19.4; I^2=0.0%, p=0.50) (Figure 18 and Table 9). Only Moon, et al. [80] studied the *HLA-B*4002 genotype* and oxcarbazepine-induced maculopapular rash by comparing cases

with either the general population [OR=4.04 (95%CI=1.83-8.90)] or with their oxcarbazepine-tolerant group [OR=4.33 (95%CI=1.36-13.8)] (Table 9).

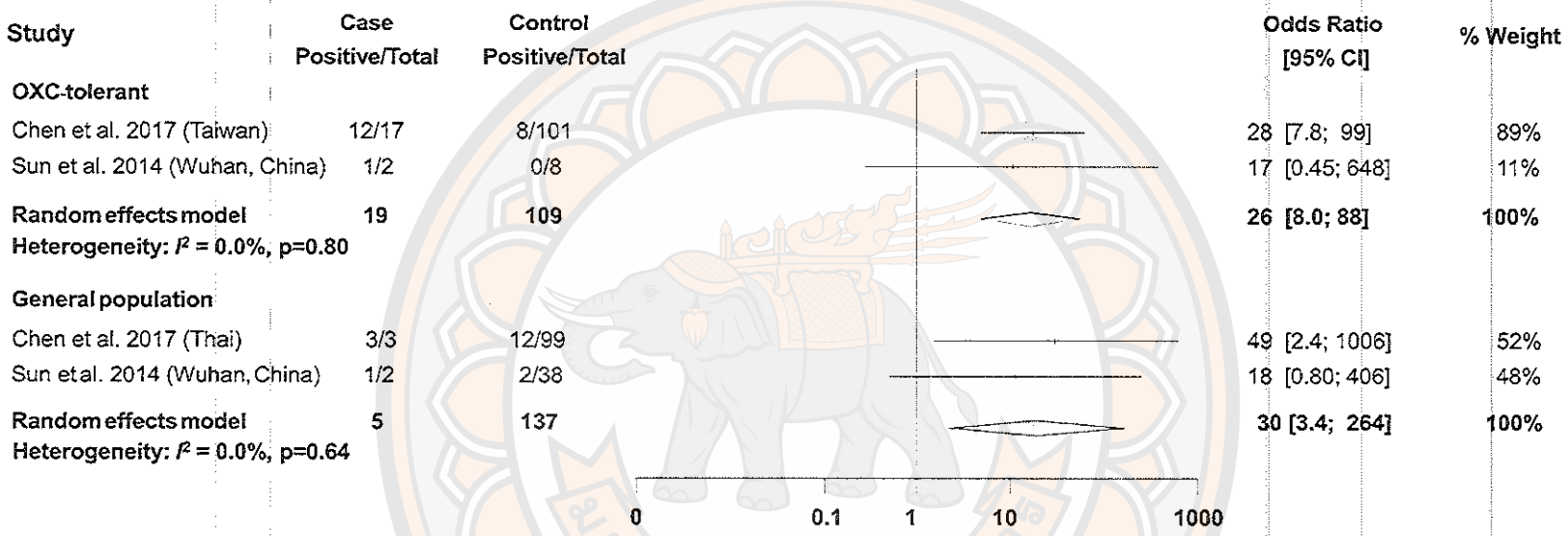

Figure 16 Forest plots of the associations between *HLA-B*1502* and oxcarbazepine-induced Stevens-Johnson syndrome

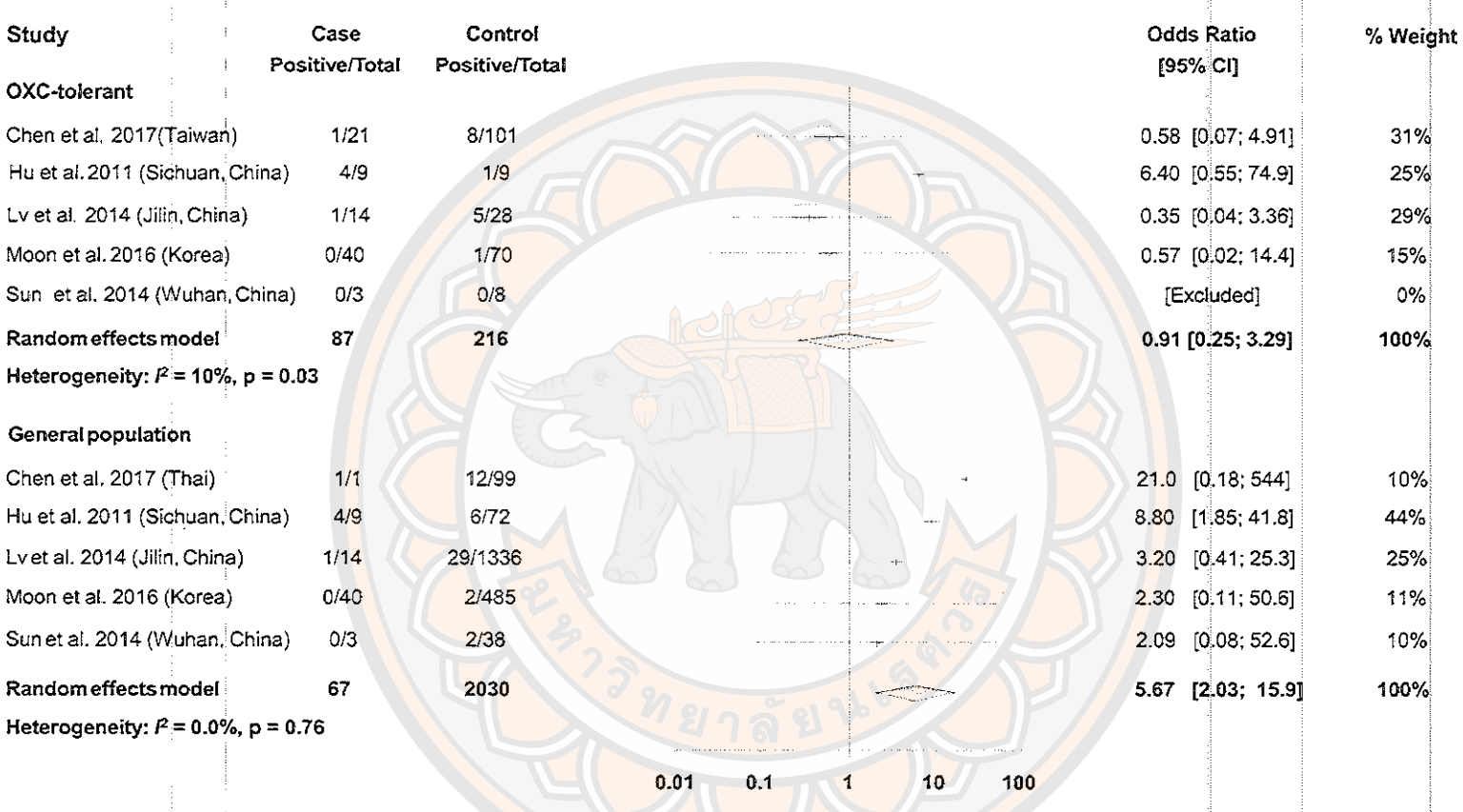

Figure 17 Forest plots of the associations between *HLA-B*1502* and oxcarbazepine-induced maculopapular rash

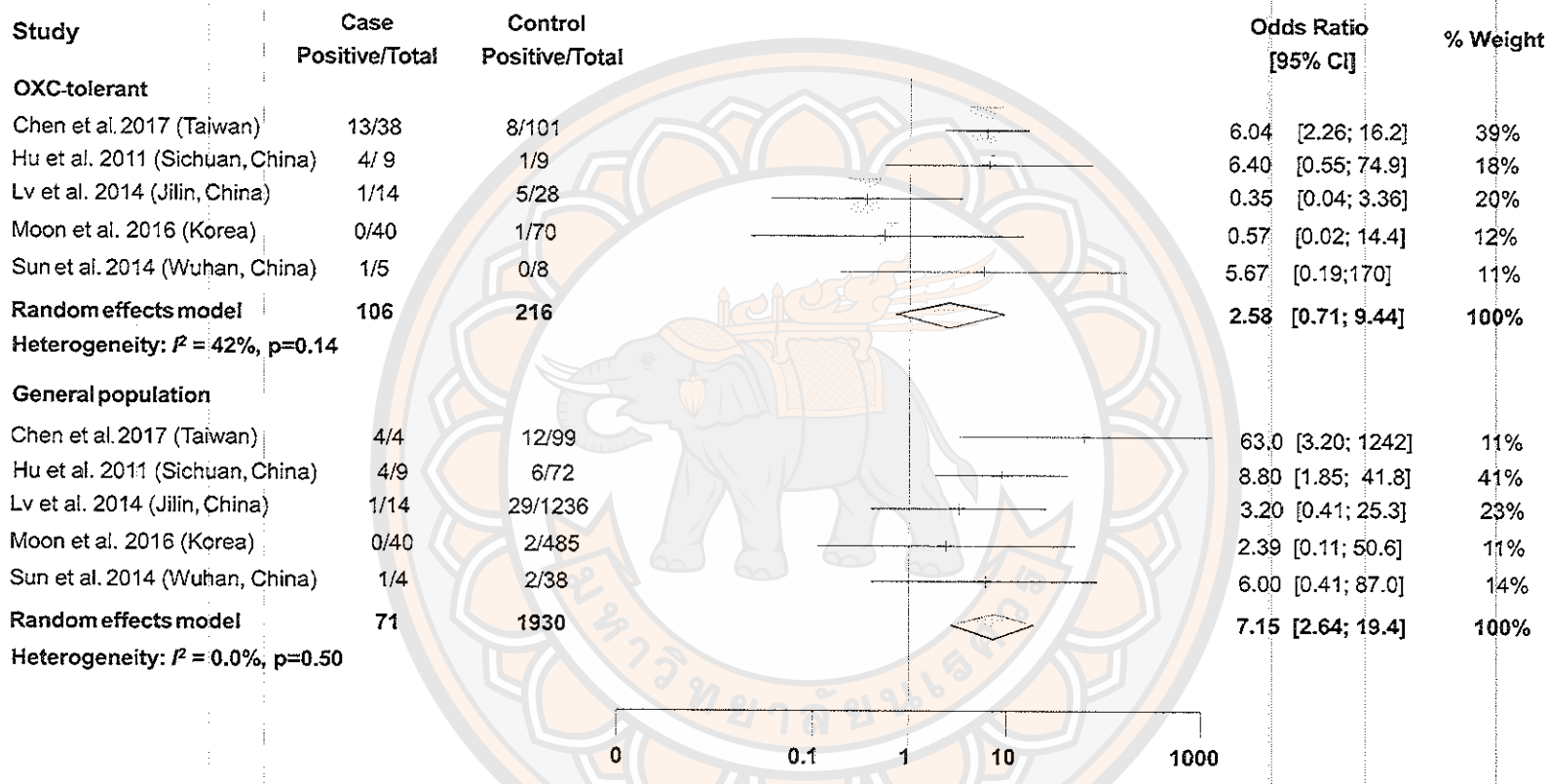

Figure 18 Forest plots of the associations between *HLA-B*1502* and oxcarbazepine-induced Stevens-Johnson syndrome and maculopapular rash

MHC class II and oxcarbazepine-induced cADRs

The associations between MHC class II and oxcarbazepine-induced cADRs are summarized in Table 9. Associations between *HLA-DQBI*0501*, *HLA-DQBI*0503*, *HLA-DRBI*0403*, *HLA-DRBI*0406*, and *HLADRBI*1405* and with oxcarbazepine-induced maculopapular rash in a Korean population were determined by Moon, et al. [80] *HLA-DRBI*0403* was associated with oxcarbazepine-induced maculopapular rash by comparing cases with either the general population or the oxcarbazepine-tolerant group as controls; OR=3.11 (95%CI=1.27-7.59) and 14.64 (95%CI=1.73-124), respectively (Table 9).

Table 9 Summary odds ratios the included studies categorized by *HLA* genotypes and oxcarbazepine-induced cADRs

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-A* genotypes**										
*HLA-A*3101*	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	6	34	2	483	38.4 (7.5-197)
		Chen et al [79]	2017	Thai (Thailand)	Case control	0	1	3	96	9.2 (0.31-268)
		Subtotal (I^2= 0.0%, P = 0.42)								**29.2 (6.7-128)[a]**
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	6	34	12	58	0.9 (0.3-2.5)
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	2	19	3	98	3.4 (0.54-22)
		Subtotal (I^2= 39%, P = 0.20)								**1.4 (0.38-5.1)**
	SJS	**General population control**								
		Chen et al [79]	2017	Thai (Thailand)	Case control	0	3	3	96	3.9 (0.17-91)
		OXC-tolerant								
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	1	16	3	98	2.0 (0.20-20)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-A* genotypes**										
HLA-A*3101	DRESS	**OXC-tolerant**								
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	0	6	3	98	2.2 (0.10-46)
	BFDE	**OXC-tolerant**								
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	0	2	3	98	5.6 (0.23-140)
HLA-A*3201	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	3	482	8.5 (1.4-52)[a]
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	1	69	3.6 (0.32-41)
HLA-A*3201	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	3	482	8.5 (1.4-52)[a]
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	1	69	3.6 (0.32-41)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
HLA-B*0705	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
HLA-B*1301	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	1	27	2.1 (0.12-36)
HLA-B*1302	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	3	11	3	32	2.9 (0.51-17)
		Lv et al [78]	2014	Han Chinese (China)	Case control	2	12	4	24	1.0 (0.16-6.3)
HLA-B*1315	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
HLA-B*1501	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	2	26	1.0 (0.08-12)
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	16	54	0.18 (0.04-0.82)
		Subtotal (I^2= 27%, P = 0.24)								**0.3 (0.06-1.6)**
		OXC-tolerant								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	3	32	0.82 (0.08-8.6)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
		General population control								
		Hu et al [29]	2011	Han Chinese (China)	Case control	4	5	6	66	8.8 (1.9-42)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	29	1207	2.1 (0.08-53)
		Sun et al [77]	2014	Han Chinese (China)	Case control	0	3	2	36	3.2 (0.4-25)
		Moon et al [80]	2016	Korean (Korea)	Case control	0	40	2	483	2.3 (0.11-51)
		Chen et al [79]	2017	Thai (Thailand)	Case control	1	0	12	87	21 (0.8-544)
				Subtotal (I^2= 0.0%, P = 0.76)						**5.7 (2.0-16)[a]**
HLA-B*1502	MP rash	**OXC-tolerant**								
		Hu et al [29]	2011	Han Chinese (China)	Case control	4	5	1	8	6.4 (0.55-75)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	5	23	0.35 (0.04-3.4)
		Sun et al [77]	2014	Han Chinese (China)	Case control	0	3	0	8	(Excluded)
		Moon et al [80]	2016	Korean (Korea)	Case control	0	40	1	69	0.57 (0.02-14)
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	1	20	8	93	0.58 (0.07-4.9)
				Subtotal (I^2= 10%, P = 0.34)						**0.91 (0.25-3.3)**

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
*HLA-B*1502*	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	2	33	1.3 (0.11-15)
	SJS	**General population control**								
		Sun et al [77]	2014	Han Chinese (China)	Case control	1	1	2	36	18 (0.90-406)
		Chen et al [79]	2017	Thai (Thailand)	Case control	3	0	12	87	49 (2.4-1006)
		Subtotal (I^2= 0.0%, P = 0.80)								**30 (3.5-264)[a]**
		OXC-tolerant								
		Sun et al [77]	2014	Han Chinese (China)	Case control	1	1	0	8	17 (0.45-648)
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	12	5	8	93	28 (7.8-99)
		Subtotal (I^2= 0.0%, P = 0.64)								**26 (8.0-88)[a]**

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
		General population control								
HLA-B*1502	MP rash+SJS	Hu et al [29]	2011	Han Chinese (China)	Case control	4	5	6	66	8.8 (1.9-42)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	29	1207	3.2 (0.41-25)
		Sun et al [77]	2014	Han Chinese (China)	Case control	1	3	2	36	6.0 (0.41-87)
		Moon et al [80]	2016	Korean (Korea)	Case control	0	40	2	483	2.4 (0.11-51)
		Chen et al [79]	2017	Thai (Thailand)	Case control	4	0	12	87	63. (3.2-1242)
				Subtotal (I^2= 0.0%, P = 0.50)						**7.2 (2.6-19)[a]**
		OXC-tolerant								
HLA-B*1502	MP rash+SJS	Hu et al [29]	2011	Han Chinese (China)	Case control	4	5	1	8	6.4 (0.55-75)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	5	23	0.35 (0.04-3.4)
		Sun et al [77]	2014	Han Chinese (China)	Case control	1	4	0	8	5.7 (0.19-170)
		Moon et al [80]	2016	Korean (Korea)	Case control	0	40	1	69	0.57 (0.02-14)
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	13	25	8	93	6.1 (2.3-16)
				Subtotal (I^2= 42%, P = 0.14)						**2.6 (0.71-9.4)**

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
HLA-B*1502	DRESS	**OXC-tolerant**								
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	0	6	8	93	2.2 (0.10-50)
	BFDE	**OXC-tolerant**								
		Chen et al [79]	2017	Han Chinese (Taiwan)	Case control	0	2	8	93	0.85 (0.04-16)
HLA-B*1511	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	1	39	19	466	0.63 (0.11-7.0)
		OXC-tolerant								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	2	26	0.37 (0.02-8.1)
		Moon et al [80]	2016	Korean (Korea)	Case control	1	39	1	69	1.8 (0.11-29)
		Subtotal (I^2= 0.0%, P = 0.46)								**0.87 (0.11-7.0)**
HLA-B*1513	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
HLA-B*1519	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
HLA-B genotypes										
		OXC-tolerant								
HLA-B*1527	MP rash	He et al [30]	2012	Han Chinese (China)	Prospective cohort	2	12	0	35	14 (0.64-316)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
		OXC-tolerant								
HLA-B*1542	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
		OXC-tolerant								
HLA-B*1558	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
		OXC-tolerant								
HLA-B*2704	MP rash	He et al [30]	2012	Han Chinese (China)	Prospective cohort	2	12	0	35	14 (0.64-316)
		OXC-tolerant								
HLA-B*2705	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
		OXC-tolerant								
HLA-B*2709	MP rash	He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
HLA-B genotypes										
*HLA-B*3508*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
*HLA-B*3531*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	2	26	0.37 (0.02-8.1)
*HLA-B*3710*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
*HLA-B*3801*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
*HLA-B*3802*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	3	11	2	25	3.4 (0.50-23)
*HLA-B*3901*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95% CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
HLA-B*3905	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)
HLA-B*4001	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	3	11	10	25	0.68 (0.16-3.0)
		Lv et al [78]	2014	Han Chinese (China)	Case control	2	12	4	24	1.0 (0.16-6.3)
HLA-B*4002	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	10	30	37	448	4.0 (1.8-8.9)[a]
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	10	30	5	65	4.3 (1.4-14)[a]
HLA-B*4006	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
HLA-B*4402	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
***HLA-B* genotypes**										
HLA-B*4403	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	2	12	4	24	1.0 (0.16-6.3)
HLA-B*4601	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	3	11	11	24	0.60 (0.14-2.6)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	3	25	0.64 (0.06-6.8)
HLA-B*4701	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
HLA-B*4801	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	4	24	0.19 (0.01-3.7)
HLA-B*4804	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	24	0.56 (0.02-15)
HLA-B*4901	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
HLA-B genotypes										
		OXC-tolerant								
HLA-B*5101	MP rash	He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	3	32	0.82 (0.08-8.6)
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	1	27	2.1 (0.12-36)
		OXC-tolerant								
HLA-B*5102	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
		OXC-tolerant								
HLA-B*5201	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
		OXC-tolerant								
HLA-B*5301	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
		OXC-tolerant								
HLA-B*5401	MP rash	He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)
		OXC-tolerant								
HLA-B*5501	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
		OXC-tolerant								
HLA-B*5502	MP rash	Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	1	27	2.1 (0.12-36)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95% CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class I										
HLA-B genotypes										
*HLA-B*5601*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	1	13	0	28	6.3 (0.24-166)
*HLA-B*5604*	MP rash	**OXC-tolerant**								
		He et al [30]	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.9 (0.30-206)
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-17)
*HLA-B*5801*	MP rash	**OXC-tolerant**								
		Lv et al [78]	2014	Han Chinese (China)	Case control	0	14	3	25	0.25 (0.01-5.21)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class II										
HLA-DQB1*0501	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	1	39	3	482	4.1 (0.42-41)
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	1	39	7	63	0.23 (0.03-2.0)
HLA-DRB1*0403	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	7	33	31	454	3.1 (1.3-7.6)[a]
HLA-DRB1*0403	MP rash	**OXC-tolerant**								
		Moon et al [80]	2016	Korean (Korea)	Case control	7	33	1	69	15 (1.7-124)[a]
HLA-DQB1*0503	MP rash	**General population control**								
		Moon et al [80]	2016	Korean (Korea)	Case control	3	37	46	439	0.77 (0.23-2.6)
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	3	37	14	56	0.31 (0.09-1.2)

Table 9 (cont.)

HLA genotypes	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)
						HLA positive	HLA negative	HLA positive	HLA negative	
MHC class II										
		General population control								
HLA-DRBI*0406	MP rash	Moon et al [80]	2016	Korean (Korea)	Case control	2	38	39	446	0.60 (0.14-2.6)
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	2	38	11	59	0.28 (0.06-1.3)
		General population control								
HLA-DRBI*1405	MP rash	Moon et al [80]	2016	Korean (Korea)	Case control	3	37	22	463	1.7 (0.49-6.0)
		OXC-tolerant								
		Moon et al [80]	2016	Korean (Korea)	Case control	3	37	11	59	0.43 (0.11-1.7)

Note: 95%CI = 95%confidence intervals; cADRs = cutaneous adverse reactions; BFDE= bullous fixed drug eruption; DRESS = drug rash with eosinophilia and systemic symptoms; HLA = human leukocyte antigen; MHC = major histocompatibility complex; MP rash = maculopapular rash; OR = odds ratio; OXC = oxcarbazepine; SJS = Stevens–Johnson syndrome

[a] Association with a statistical significant

Discussions of the oxcarbazepine

To our knowledge, this is the first systematic review and meta-analysis study to identify the associations between *HLA* genotypes and oxcarbazepine-induced cADRs. In our study, 49 different *HLA* genotypes were identified as risks of oxcarbazepine-induced cADRs but meta-analysis could be applied to only 4 of the genes (i.e., *HLA-A*3101*, *HLA-B*1501*, *HLA-B*1502*, and *HLA-B*1511*). Of these *HLA-A*3101* and *HLA-B* 1502* were associated with oxcarbazepine-induced cADRs (Figure 15-18). All of the other *HLA* genotypes and oxcarbazepine-induced cADRs are summarized in Table 3. Notably, we found associations between *HLA-B*1502* and oxcarbazepine-induced SJS in both general population control and oxcarbazepine-tolerant groups. The ORs were close to those of the general population and oxcarbazepine-tolerant control [OR=30.2 (95%CI=3.45-264) and OR=26.4 (95%CI=7.98-87.6), respectively] (Figure 16). Nonetheless, due to limited number of studies, more studies investigating associations between *HLA-B*1502* and oxcarbazepine-induced SJS/TEN are needed. In addition, *HLA-B*1502* was associated with oxcarbazepine-induced maculopapular rash in general population controls (OR=5.67, 95%CI=2.03-15.9) (Figure 17). To further investigate the associations between *HLA-B*1502* and oxcarbazepine-induced maculopapular rash and SJS, we combined oxcarbazepine-induced maculopapular rash groups with oxcarbazepine-induced SJS groups. Then, *HLA-B*1502* was associated with the oxcarbazepine-induced maculopapular rash/SJS group, comparing the general population [OR=7.15 (95%CI=2.64-19.4)] (Figure 18). Nonetheless, the association between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash was observed in general population controls [OR=29.2 (95% CI=6.70-128)] (Figure 15). Other oxcarbazepine-induced pathologies such as TEN are not well studied and, to our knowledge, are confined to studies where SJS and TEN data were pooled [28, 81, 82]. Thus, based on current findings and the previous studies, subjects harboring the allele might develop TEN when given oxcarbazepine. All of the included studies were from Han-Chinese, Thai and Korean populations [29, 30, 77, 78, 79, 80]. Whether these associations with oxcarbazepine-induced cADRs are more widespread need large-scale studies in more ethnically diverse populations. We found two studies [79, 80] that found associations between *HLA-A*3101* and oxcarbazepine-induced cADRs while for carbamazepine-

induced cADRs (i.e., maculopapular rash) other ethnicities including Caucasian and Japanese are susceptible [83, 84, 85, 86, 87, 88]. Furthermore, associations between *HLA-A*3101* and carbamazepine-induced SJS/TEN were also reported in some studies which suggests that *HLA-A*3101* could also induce oxcarbazepine-induced cADRs. Thus in further studies that we suggest using wider ethnic groups, a wider range of MHC genes should be included.

Recently, 3D molecular coupling models of HLA protein molecules and carbamazepine, oxcarbazepine and abacavir were developed [89, 90]. These models shed an understanding of how HLA molecules binds specifically to their ligands and potentially causes those adverse drug reactions (i.e., Steven-Johnson syndrome, toxic epidermal necrolysis, DRESS) [89]. Despite the structural similarities of oxcarbazepine and carbamazepine and their reported cross-reactivity, oxcarbazepine does not share the HLA related risk factors with carbamazepine-induced SJS/TEN which are 30-40 folds more than for oxcarbazepine in Han Chinese [91]. In addition, some patients carrying *HLA-B*1502* with a history of carbamazepine-induced SJS could tolerate oxcarbazepine [91]. To understand the biological basis of this phenomena, the mechanism of the cross reactivity needs further studies.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

This chapter was divided into 3 separate section as follows: 1) Dapsone; 2) Methazolamide, and; 3) Oxcarbazepine.

Section I: Dapsone

Conclusions of the dapsone

Associations between *HLA-B*1301* and dapsone-induced cADRs were identified in both dapsone-tolerant and healthy control groups. Screening for *HLA-B*1301* before initiation of dapsone therapy is warranted in Asian populations.

Recommendations of the dapsone

There were only 3 case-control studies investigating associations between *HLA-B*1301* and dapsone-induced DHS in our study [17, 19, 70]. These studies conducted in Chinese and Thai populations. To clarify the associations and evaluate its value clinically identify, further studies investigating associations between *HLA-B*1301* and dapsone-induced cADRs in other populations from other geographic areas or the same population but larger case-control studies, including dapsone-tolerant controls, or prospective studies are needed. In addition, clinical utility and cost-effectiveness of *HLA-B*1301* testing before initiation of dapsone therapy may be needed.

Section II: Methazolamide

Conclusions of the methazolamide

Strong associations between *HLA-B*5901*, *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were identified in both methazolamide-tolerant and general population controls. Therefore, genetic screening of *HLA-B*5901* and *HLA-Cw*0102* in Asian populations (i.e., Han Chinese, Koreans) prior to an initiation of methazolamide therapy is warranted.

Recommendations of the methazolamide

Since SJS/TEN are considered to be very rare disorders [92] and there were 2 studies investigating associations between associations between *HLA-B*5901, HLA-Cw*0102, HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were included in our systematic review and meta-analysis [25, 27]. These studies conducted in Korean and Han-Chinese population and 13 patients with methazolamide-induced SJS/TEN, 30 methazolamide-tolerant and 768 general population controls were included [25, 27]. Thus, a small study effect is unavoidable. The small study effect might show a larger effect than results from large studies [93].
In addition, the first case report of methazolamide-induced SJS were reported in two Japanese-American descents [47]. Several case reports of methazolamide-induced SJS/TEN in subjects carrying the *HLA-B*59* and *HLA-B*5901* were reported in Japanese, Korean and Han-Chinese population [21, 22, 23, 24, 94]. To clarify these associations, further studies investigating associations between *HLA-B*5901, HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN in other populations from other geographic areas or the same population but larger case-control studies, including methazolamide-tolerant controls, or prospective studies are needed. When another study investigating an association between the *HLA* genotypes and methazolamide-induced SJS/TEN is available, a re-analysis of the meta-analysis should be performed. Furthermore, It has been well documented that *HLA* genotypes are associated with sulphonamide-induced SJS/TEN [12, 95, 96, 97]. Other drugs with similar structures to the sulphonamide drugs (e.g. dapsone, carbonic anhydrase inhibitors) may involve in cADRs and hypersensitivity syndrome [19, 24, 98]. Interestingly, carbonic anhydrase inhibitor drugs (i.e., acetazolamide, brinzolamide and dorzolamide) -induced SJS/TEN were also reported also in Japanese, Korean and

Han-Chinese population [49, 73, 74, 75]. However, HLA genotyping was not investigated in these studies. Since all of the drugs in this class harbor a sulfone group in their chemical structures, like sulfonamides, it is possible that other drugs in this group may be able to cause cADRs including SJS/TEN. Thus, more studies investigating associations between *HLA* genotypes and carbonic anhydrase inhibitor drugs-induced cADRs are needed.

Section III: Oxcarbazepine

Conclusions of the oxcarbazepine

Strong associations between *HLA-B*1502* and oxcarbazepine-induced cADRs (SJS and maculopapular rash) were found in both controls from cases using either controls from either the general population or and oxcarbazepine-tolerant groups. In general population controls, oxcarbazepine-induced maculopapular rash was associated with *HLA-A*3101*. These strong links were detected in Korean, Han-Chinese and Thai ethnicities. Therefore, a genetic screening in these ethnicities should precede an oxcarbazepine treatment. For other populations, genetic screening of *HLA-B*1502* prior to oxcarbazepine therapy may be warranted. However, screening for a wider range of both *MHC* genotype and ethnicities should be undertaken.

Recommendations of the oxcarbazepine

There were 2 studies investigating associations between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash. Statistically significant association between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash was observed in general population controls. While for carbamazepine-induced cADRs (i.e., maculopapular rash) other ethnicities including Caucasian and Japanese are susceptible [85, 86, 87, 99, 100]. Furthermore, associations between *HLA-A*3101* and carbamazepine-induced SJS/TEN were also reported in some studies [99, 100]. Thus, *HLA-A*3101* could also induce oxcarbazepine-induced cADRs, we suggested further studies that investigating associations between *HLA-A*3101* and oxcarbazepine-induced maculopapular rash and other cADRs in wider ethnic groups are needed.

There were 2 studies investigating associations between *HLA-B*1502* and oxcarbazepine-induced SJS [77, 79]. The association between *HLA-B*1502* and oxcarbazepine-induced TEN are not well understood. Due to limit numbers of studies and types of cADRs, more studies with other oxcarbazepine-induced pathologies such as TEN and large-scale studies in more ethnically diversed populations are needed.

A recent meta-analysis study determining associations between *HLA-B*1502* and oxcarbazepine-induced cADRs was reported by Liu et al. [101].

There were several difference between Liu et al. study [101] and our current study. Those included;

1. Objective of the study

Our study aimed to identify associations between *HLA* genotypes and oxcarbazepine-induced cADRs. Whereas, Liu et al. aimed to identify associations between *HLA-B*1502* and oxcarbazepine-induced cADRs [101] .

2. Databases used to acquire relevant studies

In our study, a comprehensive and systematic search were performed from the inception of the following databases: PubMed/Medline (U.S. National Library of Medicine, Bethesda, MD, USA), HuGENet (Human Genome Epidemiology Network), and Cochrane library. Whereas, Liu et al. performed systematic search in EMBASE, PubMed, The Cochrane Library and CNKI (China National Knowledge Infrastructure) [101].

3. Numbers of the included studies

There were 2 studies [Hung et al. (2010) [102] and He et al. (2012) [30]] were excluded from our meta- analysis. Whereas, Liu et al. [101] included these 2 studies. There were some duplicate population between Hung et al. (2010) [102] and Chen et al. (2017) [79]. All of our included studies were case-control studies while He et al. (2012) [30] was a cohort study. Thus, He et al. (2012) [30] was excluded from our analysis. In addition, Liu et al. [101] included Xiang et al. (2016) Wu et al. (2015) which can identify from Chinese database.

4. Results

In Liu et al. study, the number of positive *HLA-B*1502* in oxcarbazepine-tolerant control from Sun et al [77] was 2. Whereas, we identified none of positive *HLA-B*1502* in oxcarbazepine-tolerant control.

Different number of positive *HLA-B*1502*/the number of total in oxcarbazepine-induced cADRs from Chen et al. (2017) [79] were reported (i.e., 2/22 and 2/24) in Liu et al. study. Actually, number of positive *HLA-B*1502*/the number of total in oxcarbazepine-induced cADRs from Chen et al. (2017) [79] was 2/22.

Implementation and future directions from this study

As for the future direction, more epidemiology studies are needed to clarify and evaluate its clinical value of these associations. Furthermore, to identify association *HLA* genotypes and drug-induced ADRs in other populations, epidemiology studies from other geographic areas are needed.

Clinical utility and cost-effectiveness of *HLA* genotypes testing studies may be needed in some countries. Other directions are *in silico* modeling studies of drug-HLA protein binding. Then, ability of drug-HLA protein complex on activating T-cell and mechanisms by which *HLA* genotypes can cause drugs-induced ADRs studies are required. In addition, Mechanism/factors involving drug-induced ADRs in patients with negative *HLA* genotypes and preventing of drug-induced ADRs in patients with positive *HLA* genotypes studies may be needed.

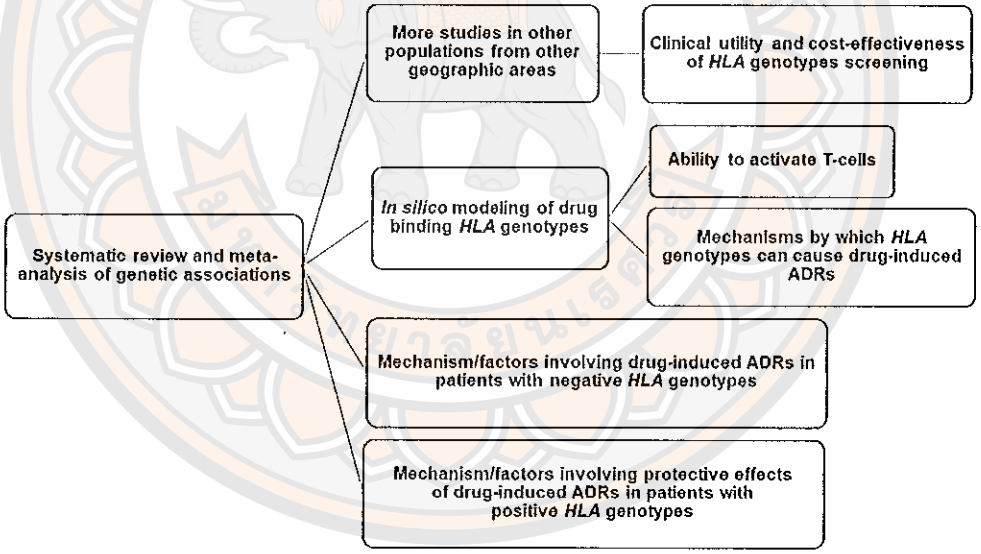

Figure 19 Implementation and future directions from this study

REFERENCES

REFERENCES

[1] Roujeau, J.C., & Stern, R.S. (1994). Severe adverse cutaneous reactions to drugs. *N Engl J Med, 331*(19), 1272-1285. doi:10.1056/nejm199411103311906

[2] Lerch, M., Mainetti, C., & Terziroli Beretta-Piccoli, B. (2017). Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Rev Allergy Immunol., 54*(1), 147-176. doi:10.1007/s12016-017-8654-zdoi:10.1007/s12016-017-8654-z

[3] Ergen, E.N., & Hughey, L.C. (2017). Stevens-Johnson syndrome and toxic epidermal necrolysis. *JAMA Dermatol, 153*(12), 1344. doi:10.1001/jamadermatol.2017.3957

[4] Roujeau, J.C. (2005). Clinical heterogeneity of drug hypersensitivity. *Toxicology, 209*(2), 123-129. doi:10.1016/j.tox.2004.12.022

[5] Dodiuk-Gad, R.P., Chung, W.H., Valeyrie-Allanore, L., & Shear, N.H. (2015). Stevens-Johnson syndrome and toxic epidermal necrolysis: An update. *Am J Clin Dermatol, 16*(6), 475-493. doi:10.1007/s40257-015-0158-0

[6] Oliveira, A., Sanches, M., & Selores, M. (2011). Stevens-Johnson syndrome and toxic epidermal necrolysis. *Acta Med Port, 24 Suppl 4*, 995-1002.

[7] Arantes, L.B., Reis, C.S., Novaes, A.G., Carvalho, M.R., Gottems, L.B.D., & Novaes, M. (2017). Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiological and clinical outcomes analysis in public hospitals. *An Bras Dermatol, 92*(5), 661-667. doi:10.1590/abd1806-4841.20176610

[8] Bharadwaj, M., Illing, P., & Kostenko, L. (2010). Personalized medicine for HLA-associated drug-hypersensitivity reactions. *Personalized Medicine, 7*(5), 495-516. doi:10.2217/pme.10.46

[9] Lonjou, C., Borot, N., Sekula, P., Ledger, N., Thomas, L., Halevy, S., . . . Mockenhaupt, M. (2008). A European study of HLA-B in Stevens-

Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics, 18*(2), 99-107. doi:10.1097/FPC.0b013e3282f3ef9c

[10] Illing, P.T., Purcell, A.W., & McCluskey, J. (2017). The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions. *Immunogenetics, 69*(8-9), 617-630. doi:10.1007/s00251-017-1007-5

[11] Chung, W., Hung, S., & Chen, Y. (2007). Human leukocyte antigens and drug hypersensitivity. *Current Opinion in Allergy & Clinical Immunology, 7*(4), 317-323.

[12] Kongpan, T., Mahasirimongkol, S., Konyoung, P., Kanjanawart, S., Chumworathayi, P., Wichukchinda, N., . . . Tassaneeyakul, W. (2015). Candidate HLA genes for prediction of co-trimoxazole-induced severe cutaneous reactions. *Pharmacogenet Genomics, 25*(8), 402-411. doi:10.1097/fpc.0000000000000153

[13] Rufini, S., Ciccacci, C., Politi, C., Giardina, E., Novelli, G., & Borgiani, P. (2015). Stevens-Johnson syndrome and toxic epidermal necrolysis: an update on pharmacogenetics studies in drug-induced severe skin reaction. *Pharmacogenomics, 16*(17), 1989-2002. doi:10.2217/pgs.15.128

[14] Somkrua, R., Eickman, E.E., Saokaew, S., Lohitnavy, M., & Chaiyakunapruk, N. (2011). Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet, 12*, 118. doi:10.1186/1471-2350-12-118

[15] Tangamornsuksan, W., Lohitnavy, O., Kongkaew, C., Chaiyakunapruk, N., Reisfeld, B., Scholfield, N.C., & Lohitnavy, M. (2015). Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. *J Pharm Pharm Sci, 18*(1), 68-76.

[16] Tangamornsuksan, W., Chaiyakunapruk, N., Somkrua, R., Lohitnavy, M., & Tassaneeyakul, W. (2013). Relationship between the HLA-B*1502

allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol, 149*(9), 1025-1032. doi:10.1001/jamadermatol.2013.4114

[17] Wang, H., Yan, L., Zhang, G., Chen, X., Yang, J., Li, M., . . . Wang, B. (2013). Association between HLA-B*1301 and dapsone-induced hypersensitivity reactions among leprosy patients in China. *J Invest Dermatol, 133*(11), 2642-2644. doi:10.1038/jid.2013.192

[18] Zhang, F.R., Liu, H., Irwanto, A., Fu, X.A., Li, Y., Yu, G.Q., . . . Liu, J.J. (2013). HLA-B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med, 369*(17), 1620-1628. doi:10.1056/NEJMoa1213096

[19] Tempark, T., Satapornpong, P., Rerknimitr, P., Nakkam, N., Saksit, N., Wattanakrai, P., . . . Sukasem, C. (2017). Dapsone-induced severe cutaneous adverse drug reactions are strongly linked with HLA-B*13: 01 allele in the Thai population. *Pharmacogenet Genomics, 27*(12), 429-437. doi:10.1097/fpc.0000000000000306

[20] Xu Y., Wu, M., Sheng, F., & Sun Q.. (2015). Methazolamide-induced toxic epidermal necrolysis in a Chinese woman with HLA-B5901. *Indian J Ophthalmol, 63*(7), 623-624. doi:10.4103/0301-4738.167105

[21] Shu, C., Shu, D., Tie, D., Yu, M., Zhang, R., Wang, T., . . . Yan, Y. (2015). Toxic epidermal necrolysis induced by methazolamide in a Chinese-Korean man carrying HLA-B*59:01. *Int J Dermatol, 54*(11), 1242-1245. doi:10.1111/ijd.12651

[22] Shirato, S., Kagaya, F., Suzuki, Y., & Joukou, S. (1997). Stevens-Johnson syndrome induced by methazolamide treatment. *Arch Ophthalmol, 115*(4), 550-553.

[23] Moon, J.I., Seo, J.H., & Park, C.K. (2000). Association of HLA type with Stevens - Johnson syndrome induced by methazolamide treatment. *J Korean Ophthalmol Soc, 41*, 2241.

[24] Sung K.H., Jeong, Y., Choi, H.U., & Lee, S.K. (2005). Two cases of HLA-B59(+) Stevens-Johnson syndrome-toxic epidermal necrolysis associated with methazolamide treatment. *Korean J Dermatol, 43*, 561-563.

[25] Kim, S.H., Kim, M., Lee, K.W., Kim, S.H., Kang, H.R., Park, H.W., & Jee, Y.K. (2010). HLA-B*5901 is strongly associated with methazolamide-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Pharmacogenomics, 11*(6), 879-884. doi:10.2217/pgs.10.54

[26] Yang, F., Yang, Y., Zhu, Q., Chen, S.A., Fu, X., Yan, S., . . . Xing, Q. (2015). Research on susceptible genes and immunological pathogenesis of cutaneous adverse drug reactions in Chinese Hans. *J Investig Dermatol Symp Proc, 17*(1), 29-31. doi:10.1038/jidsymp.2015.6

[27] Yang, F., Xuan, J., Chen, J., Zhong, H., Luo, H., Zhou, P., . . . Xing, Q. (2016). HLA-B*59:01: a marker for Stevens-Johnson syndrome/toxic epidermal necrolysis caused by methazolamide in Han Chinese. *Pharmacogenomics J, 16*(1), 83-87. doi:10.1038/tpj.2015.25

[28] Hung, S.I., Chung, W.H., Liu, Z.S., Chen, C.H., Hsih, M.S., Hui, R.C., . . . Chen, Y.T. (2010 Mar). Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics, 11*(3), 349-356. doi:10.2217/pgs.09.162

[29] Hu, F., Wu, X., An, D., Yan, B., Stefan, H., & Zhou, D. (2011 Mar). Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population. *Seizure, 20*(2), 160-162. doi:10.1016/j.seizure.2010.11.014

[30] He, N., Min, F.L., Shi, Y.W., Guo, J., Liu, X.R., Li B.M., . . . Liao, W.P. (2012). Cutaneous reactions induced by oxcarbazepine in Southern Han Chinese: Incidence, features, risk factors and relation to HLA-B alleles. *Seizure, 21*(8), 614-618. doi:10.1016/j.seizure.2012.06.014

[31] Sun, D., Yu, C.H., Liu, Z.S., He, X.L., Hu, J.S., Wu, G.F., . . . Xiang, H.H. (2014 Feb). 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, 34*(1), 146-150. doi:10.1007/s11596-014-1247-7

[32] Zhang, J., Li, X., Su, Y., Sun, M., Wang, J., & Hao, Y. (2018). Association between HLA gene polymorphism and cutaneous adverse reactions caused by antiepileptic drugs. *Experimental and Therapeutic Medicine, 15*(4), 3399-3403. doi:10.3892/etm.2018.5801

[33] Horton, R., Wilming, L., Rand, V., Lovering, R.C., Bruford, E.A., Khodiyar, V.K., . . . Beck, S. (2004). Gene map of the extended human MHC. *Nat Rev Genet, 5*(12), 889-899. doi:10.1038/nrg1489

[34] Sullivan, A., Watkinson, J., Waddington, J., Park, B.K., & Naisbitt, D.J. (2018). Implications of HLA-allele associations for the study of type IV drug hypersensitivity reactions. *Expert Opin Drug Metab Toxicol, 14*(3), 261-274. doi:10.1080/17425255.2018.1441285

[35] Abbas, A., & Lichtman, A.H. (2006). *Basic immunology: functions and disorders of the immune system* (2nd ed.). Philadelphia: Elsevier.

[36] Zhu, Y.I., & Stiller, M.J. (2001). Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol, 45*(3), 420-434. doi:10.1067/mjd.2001.114733

[37] Kannan, G., Vasantha, J., Rani, N.V., Thennarasu, P., Kousalya, K., Anuradha, P., & Reddy, C.U. (2009). Drug usage evaluation of dapsone. *Indian J Pharm Sci, 71*(4), 456-460. doi:10.4103/0250-474x.57301

[38] Wozel, G., & Blasum, C. (2014). Dapsone in dermatology and beyond. *Arch Dermatol Res, 306*(2), 103-124. doi:10.1007/s00403-013-1409-7

[39] Vinod, K.V., Arun, K., & Dutta, T.K. (2013). Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy. *J Pharmacol Pharmacother, 4*(2), 158-160. doi:10.4103/0976-500x.110917

[40] Kosseifi, S.G., Guha, B., Nassour, D.N., Chi, D.S., & Krishnaswamy, G. (2006). The Dapsone hypersensitivity syndrome revisited: a potentially fatal multisystem disorder with prominent hepatopulmonary manifestations. *J Occup Med Toxicol, 1*, 9. doi:10.1186/1745-6673-1-9

[41] Lorenz, M., Wozel, G., & Schmitt, J. (2012). Hypersensitivity reactions to dapsone: a systematic review. *Acta Derm Venereol, 92*(2), 194-199. doi:10.2340/00015555-1268

[42] Pandey, B., Shrestha, K., Lewis, J., Hawksworth, R.A., & Walker, S.L. (2007). Mortality due to dapsone hypersensitivity syndrome complicating multi-drug therapy for leprosy in Nepal. *Trop Doct, 37*(3), 162-163. doi:10.1258/004947507781524700

[43] Tian, W., Shen, J., Zhou, M., Yan, L., & Zhang, G. (2012). Dapsone hypersensitivity syndrome among leprosy patients in China. *Lepr Rev, 83*(4), 370-377.

[44] Maren, T.H., Haywood, J.R., Chapman, S.K., & Zimmerman, T.J. (1977). The pharmacology of methazolamide in relation to the treatment of glaucoma. *Invest Ophthalmol Vis Sci, 16*(8), 730-742.

[45] Kim, S., Thiessen, P.A., Bolton, E.E., Chen, J., Fu, G., Gindulyte, A., . . . Bryant, S.H. PubChem Compound Database. Retrieved December 21, 2017, from National Center for Biotechnology Information https://pubchem.ncbi.nlm.nih.gov/compound/4100

[46] Rijal, J.P., Pompa, T., Giri, S., & Bhatt, V.R. (2014). A case of toxic epidermal necrolysis caused by trimethoprim-sulfamethoxazole. *BMJ Case Rep, 2014*. doi:10.1136/bcr-2013-203163

[47] Flach, A.J., Smith, R.E., & Fraunfelder, F.T. (1995). Stevens-Johnson syndrome associated with methazolamide treatment reported in two Japanese-American women. *Ophthalmology, 102*(11), 1677-1680.

[48] Cotter, J.B. (1998). Methazolamide-induced Stevens-Johnson syndrome: a warning!. *Arch Ophthalmol, 116*(1), 117.

[49] Her, Y., Kil, M.S., Park, J.H., Kim, C.W., & Kim, S.S. (2011). Stevens-Johnson syndrome induced by acetazolamide. *J Dermatol, 38*(3), 272-275. doi:10.1111/j.1346-8138.2010.00921.x

[50] Carroll, O.M., Bryan, P.A., & Robinson, R.J. (1966). Stevens-Johnson syndrome associated with long-acting sulfonamides. *Jama, 195*(8), 691-693.

[51] Kalis, M.M., & Huff, N.A. (2001 May). Oxcarbazepine, an antiepileptic agent. *Clin Ther, 23*(5), 680-700.

[52] McAuley, J., Biederman, T., Smith, J., & Moore, J. (2002 Jan). Newer therapies in the drug treatment of epilepsy. *Ann Pharmacother, 36*(1), 119-129.

[53] Yang, C.Y., Dao, R.L., Lee, T.J., Lu, C.W., Yang, C.H., Hung, S.I., & Chung, W.H. (2011 Dec 6). Severe cutaneous adverse reactions to antiepileptic drugs in Asians. *Neurology, 77*(23), 2025-2033. doi:10.1212/WNL.0b013e31823b478c

[54] Wang, X.Q., Lang, S.Y., Shi, X.B., Tian, H.J., Wang, R.F., & Yang, F. (2010). Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. *Seizure, 19*(9), 562-566. doi:10.1016/j.seizure.2010.09.003

[55] Hirsch, L.J., Arif, H., Nahm, E.A., Buchsbaum, R., Resor, S.R.J., & Bazil, C.W. (2008 Nov 4). Cross-sensitivity of skin rashes with antiepileptic drug use. *Neurology, 71*(19), 1527-1534. doi:10.1212/01.wnl.0000334295.50403.4c

[56] Alvestad, S., Lydersen, S., & Brodtkorb, E. (2008 Aug). Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. *Epilepsy Res, 80*(2-3), 194-200. doi:10.1016/j.eplepsyres.2008.04.003

[57] Cochrane handbook for systematic reviews of interventions version 5.1.0. (2011). *Chapter 8: Assessing risk of bias in included studies.* Retrieved from www.cochrane-handbook.org.

[58] Zlowodzki, M., Poolman, R.W., Kerkhoffs, G.M., Tornetta, P., & Bhandari, M. (2007). How to interpret a meta-analysis and judge its value as a guide for clinical practice. *Acta Orthop, 78*(5), 598-609. doi:10.1080/17453670710014284

[59] Callcut, R.A., & Branson, R.D. (2009). How to read a review paper. *Respir Care, 54*(10), 1379-1385.

[60] Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care, 2*(1), 9-14. doi:10.4103/2249-4863.109934

[61] Manchikanti, L. (2008). Evidence-based medicine, systematic reviews, and guidelines in interventional pain management, part I: introduction and general considerations. *Pain Physician, 11*(2), 161-186.

[62] Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2011). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[63] Szumilas, M. (2010). Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry, 19*(3), 227-229.

[64] DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials, 7*(3), 177-188.

[65] Higgins, J., & Thompson, S. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med, 21*(11), 1539-1558.

[66] Higgins, J.P., Thompson, S.G., Deeks, J.J., & Altman, D.G. (2003 Sep 6). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560.

[67] Begg, C., & Berlin, J. (1989). Publication bias and dissemination of clinical research. *J Natl Cancer Inst, 81*(2), 107-115.

[68] Egger, M., & Smith, G. (1998). Bias in location and selection of studies. *BMJ, 316*(7124), 61-66.

[69] Duval, S., & Tweedie, R. (2000 Jun). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

[70] Zhang, F.R., Liu, H., Irwanto, A., Fu, X.A., Li, Y., Yu, G.Q., . . . Liu, J.J. (2013). HLA-B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med, 369*(17), 1620-1628. doi:10.1056/NEJMoa1213096

[71] Gonzalez-Galarza, F.F., Takeshita, L.Y., Santos, E.J., Kempson, F., Maia, M.H., da Silva, A.L., . . . Middleton, D. (2015). Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res, 43*(Database issue), D784-788. doi:10.1093/nar/gku1166

[72] Watanabe, H., Watanabe, Y., Tashiro, Y., Mushiroda, T., Ozeki, T., Hashizume, H., . . . Kusakabe, Y. (2017). A docking model of dapsone bound to HLA-B*13:01 explains the risk of dapsone hypersensitivity syndrome. *J Dermatol Sci*. doi:10.1016/j.jdermsci.2017.08.007

[73] Kim, J.W., & Shin, S.Y. (2009). Toxic epidermal necrolysis and Stevens-Johnson syndrome caused by topical ophthalmic use of dorzolamid. *Korean J Dermatol, 27*(3), 317-321.

[74] Lee, J.H., Lee, S.J., & Kim, Y.H. (1998). A case of Stevens-Johnson syndrome after acetazolamide use. *J. Korean Ophthalmol. Soc., 39*(1), 216-220

[75] Chun, J.S., Yun, S.J., Lee, J.B., Kim, S.J., Won, Y.H., & Lee, S.C. (2008). Toxic epidermal necrolysis induced by the topical carbonic anhydrase inhibitors brinzolamide and dorzolamide. *Ann Dermatol, 20*(4), 260-262. doi:10.5021/ad.2008.20.4.260

[76] Moon, J., Kim, T., Lim, J., Sunwoo, J., Byun, J., Lee, S., . . . Lee, S. (2016). HLA-B*40:02 and DRB1*04:03 are risk factors for oxcarbazepine-induced maculopapular eruption. *Epilepsia, 57*(11), 1879-1886. doi:10.1111/epi.13566

[77] Sun, D., Yu, C.H., Liu, Z.S., He, X.L., Hu, J.S., Wu, G.F., . . . Xiang, H.H. (2014 Feb). 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, 34*(1), 146-150. doi:10.1007/s11596-014-1247-7

[78] Lv, Y.D., Min, F.L., Liao, W.P., He, N., Zeng, T., M,a D.H., & Shi, Y.W. (2013 Jul 8). The association between oxcarbazepine-induced maculopapular eruption and HLA-B alleles in a northern Han Chinese population. *BMC Neurol, 13*, 75. doi:10.1186/1471-2377-13-75

[79] Chen, C.B., Hsiao, Y.H., Wu, T., Hsih, M.S., Tassaneeyakul, W., Jorns, T.P., . . . Taiwan Severe Cutaneous Adverse Reaction Consortium. (2017). Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. *Neurology, 88*(1), 78-86. doi:10.1212/WNL.0000000000003453

[80] Moon, J., Kim, T.J., Lim, J.A., Sunwoo, J.S., Byun, J.I., Lee, S.T., . . . Lee, S.K. (2016 Nov). HLA-B*40:02 and DRB1*04:03 are risk factors for oxcarbazepine-induced maculopapular eruption. *Epilepsia, 57*(11), 1879-1886. doi:10.1111/epi.13566

[81] Nguyen, D., Chu, H.C., Nguyen, D.V., Phan, M.H., Craig, T., Baumgart, K., & van Nunen, S. (2015 Apr). HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac Allergy, 5*(2), 68-77. doi:10.5415/apallergy.2015.5.2.68

[82] Tangamornsuksan, W., Chaiyakunapruk, N., Somkrua, R., Lohitnavy, M., & Tassaneeyakul, W. (2013 Sep 1). Relationship Between the HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. *JAMA Dermatol, 149*(9), 1025-1032.

[83] Genin, E., Chen, D.P, Hung, S.I., Sekula, P., Schumacher, M., Chang, P.Y., . . . Roujeau, J.C. (2014 Jun). HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. *Pharmacogenomics J, 14*(3), 281-288.

[84] Ozeki, T., Mushiroda, T., Yowang, A., Takahashi, A., Kubo, M., Shirakata, Y., . . . Nakamura, Y. (2011 Mar 1). Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet, 20*(5), 1034-1041.

[85] Ozeki, T., Mushiroda, T., Yowang, A., Takahashi, A., Kubo, M., Shirakata, Y., . . . Nakamura, Y. (2011 Mar 1). Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet, 20*(5), 1034-1041.

[86] Hung, S.I., Chung, W.H., Jee, S.H., Chen, W.C., Chang, Y.T., Lee, W.R., . . . Chen, Y.T. (2006 Apr). Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics, 16*(4), 297-306.

[87] Amstutz, U., Ross, C.J., Castro-Pastrana, L.I., Rieder, M.J., Shear, N.H., Hayden, M.R., & Carleton, B.C. (2013 Jul). HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther, 94*(1), 142-149.

[88] McCormack, M., Alfirevic, A., Bourgeois, S., Farrell, J., Kasperavičiūtė, D., Carrington, M., . . . Pirmohamed, M. (2011 Mar 24). HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med, 364*(12), 1134-1143. doi:10.1056/NEJMoa1013297

[89] Teh, L.K., Selvaraj, M., Bannur, Z., Ismail, M.I., Rafia, H., Law, W.C., . . . Salleh, M.Z. (2016). Coupling Genotyping and Computational Modeling in Prediction of Anti-epileptic Drugs that cause Stevens Johnson Syndrome and Toxic Epidermal Necrolysis for Carrier of HLA-B*15:02. *J Pharm Pharm Sci, 19*(1), 147-160.

[90] Illing, P.T., Vivian, J.P., Dudek, N.L., Kostenko, L., Chen, Z., Bharadwaj, M., . . . McCluskey, J. (2012 Jun 28). Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature, 486*(7404), 554-558.

[91] Chen, Y.C., Chu, C.Y., & Hsiao, C.H. (2009). Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with HLA-B*1502 genotype. *J Eur Acad Dermatol Venereol, 23*(6), 702-703. doi:10.1111/j.1468-3083.2008.02988.x

[92] Harr, T., & French, L.E. (2010). Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis, 5*, 39. doi:10.1186/1750-1172-5-39

[93] Sterne, J.A., Gavaghan, D., & Egger, M. (2000). Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol, 53*(11), 1119-1129.

[94] Cheon, M., Lee, Y.B., Yu, D.S., & Kim, J.W. (2014). Toxic Epidermal Necrolysis in a Patient with HLA-B*5901 Haplotype Caused by Topical and Oral Carbonic Anhydrase Inhibitors. *Ann Dermatol, 26*(5), 645-646. doi:10.5021/ad.2014.26.5.645

[95] Roujeau, J.C., Bracq, C., Huyn, N.T., Chaussalet, E., Raffin, C., & Duedari, N. (1986). HLA phenotypes and bullous cutaneous reactions to drugs. *Tissue Antigens, 28*(4), 251-254.

[96] Roujeau, J.C., Huynh, T.N., Bracq, C., Guillaume, J.C., Revuz, J., & Touraine, R. (1987). Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol, 123*(9), 1171-1173.

[97] Mondino, B.J., Brown, S.I., & Biglan, A.W. (1982). HLA antigens in Stevens-Johnson syndrome with ocular involvement. *Arch Ophthalmol, 100*(9), 1453-1454.

[98] Tangamornsuksan, W., & Lohitnavy, M. (2018). Association Between HLA-B*1301 and Dapsone-Induced Cutaneous Adverse Drug Reactions: A Systematic Review and Meta-analysis. *JAMA Dermatol, 154*(4), 441-446. doi:10.1001/jamadermatol.2017.6484

[99] Genin, E., Chen, D.P., Hung, S.I., Sekula, P., Schumacher, M., Chang, P.Y., . . . Roujeau, J.C. (2014 Jun). HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. *Pharmacogenomics J, 14*(3), 281-288.

[100] McCormack, M., Alfirevic, A., Bourgeois, S., Farrell, J.J., Kasperavičiūtė, D., Carrington, M., . . . Pirmohamed, M. (2011 Mar 24). HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med, 364*(12), 1134-1143. doi:10.1056/NEJMoa1013297

[101] Liu, Y., Yu, Y., Nie, X., Zhao, L., & Wang, X. (2018). Association between HLA-B*15:02 and oxcarbazepine-induced cutaneous adverse reaction: a meta-analysis. *Pharmacogenomics, 19*(6), 547-552. doi:10.2217/pgs-2017-0189

[102] Hung, S.I., Chung, W.H., Liu, Z.S., Chen, C.H., Hsih, M.S., Hui, R.C., ... Chen, Y.T. (2010). Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics, 11*(3), 349-356. doi:10.2217/pgs.09.162

APPENDIXS

APPENDIX A PUBLICATION OF *HLA-B*1301* AND DAPSONE-INDUCED CUTANEOUS ADVERSE DRUGS REACTIONS

JAMA Dermatology | Original Investigation

Association Between *HLA-B*1301* and Dapsone-Induced Cutaneous Adverse Drug Reactions
A Systematic Review and Meta-analysis

Wimonchat Tangamornsuksan, MS; Manupat Lohitnavy, PhD

IMPORTANCE Dapsone-induced hypersensitivity syndrome (DHS) is a life-threatening adverse drug reaction. Based on available epidemiologic studies, HLA genotypes may play an important role in DHS.

OBJECTIVE To assess the association between *HLA-B*1301* and dapsone-induced cutaneous adverse drug reactions (cADRs).

DATA SOURCES Human studies investigating associations between *HLA-B*1301* and dapsone-induced cADRs were systematically searched without language restriction from the inception of each database until September 12, 2017, in PubMed, the Human Genome Epidemiology Network), and the Cochrane Library. Combinations of *HLA genotypes, dapsone,* and synonymous terms were used; reference lists were searched in selected articles.

STUDY SELECTION Two reviewers identified studies investigating the associations between *HLA-B*1301* and dapsone-induced cADRs that reported sufficient data for calculating the frequency of *HLA-B*1301* carriers among case and control patients, in which all patients received dapsone before *HLA-B*1301* screening. An initial search of the databases identified 391 articles, of which 3 studies (2 in Chinese populations and 1 in a Thai population) met the inclusion criteria.

DATA EXTRACTION AND SYNTHESIS Overall odds ratios (ORs) with 95% CIs were calculated using a random-effects model to determine the association between *HLA-B*1301* and dapsone-induced cADRs. Subgroup analyses by type of cADR were also performed. PRISMA guidelines were used to abstract and assess data.

MAIN OUTCOMES AND MEASURES Primary outcomes were associations between *HLA-B*1301* and dapsone-induced cADRs in dapsone-tolerant controls. The outcomes are reported as overall OR. Statistical heterogeneity was assessed using the *Q* statistic and *P* tests.

RESULTS From the 3 included studies, there were 111 unique patients with dapsone-induced cADRs (subsequently used in the meta-analysis), 1165 dapsone-tolerant patients, and 3026 healthy controls. The cases included 64 men and 49 women (2 patients were missing from the meta-analysis; 1 each from 2 of the 3 studies); mean age was 39.7 years. An association between *HLA-B*1301* and dapsone-induced cADRs was identified (summary OR, 43.0; 95% CI, 24.0-77.2). Subgroup analyses among types of cADRs produced similar findings in DHS (OR, 51.7; 95% CI, 16.9-158.9), dapsone-induced severe cADRs (Stevens-Johnson syndrome and toxic epidermal necrolysis [SJS/TEN] plus drug rash [adverse skin reaction to a drug] along with eosinophilia and systemic symptoms [DRESS]) (OR, 54.0; 95% CI, 8.0-366.2), dapsone-induced SJS/TEN (OR, 40.5; 95% CI, 2.8-591.0), and dapsone-induced DRESS (OR, 60.8; 95% CI, 7.4-496.2). There was no heterogeneity (I^2 = 0%, P = .38).

CONCLUSIONS AND RELEVANCE Associations between *HLA-B*1301* and dapsone-induced cADRs were found in dapsone-tolerant and healthy control groups. For patient safety, genetic screening for *HLA-B*1301* in Asian populations before dapsone therapy is warranted.

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Dapsone is an antimicrobial anti-inflammatory drug widely used in the treatment of some diseases.[1] As an antimicrobial agent, dapsone has been used to treat leprosy and actinomycetoma and for prophylaxis and treatment of *Pneumocystis carinii* pneumonia and malaria. It has also been used as an anti-inflammatory agent to treat dermatologic conditions, including dermatitis herpetiformis, linear IgA dermatosis, and pustular psoriasis.[2,3] Dapsone has pharmacologic (eg, hemolytic anemia, methemoglobinemia, and agranulocytosis) and idiosyncratic (dapsone-induced hypersensitivity syndrome [DHS]) adverse effects.[1] Idiosyncratic adverse effects of dapsone range from mild cutaneous reactions to severe life-threatening reactions, such as exfoliated dermatitis, liver failure, agranulocytosis, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), nephritis, and renal failure.[4,5] Dapsone-induced hypersensitivity syndrome is a life-threatening drug reaction with a mortality rate of 9.9% to 12.5%.[6-8] It is characterized by fever, adverse skin reaction to a drug, and systematic involvement and usually manifests in the first 6 weeks after dapsone treatment initiation. However, HLA genotypes are a family of genes involved in immune reactions. HLA genotypes are the most polymorphic gene cluster in the human genome.[9,10] Specific polymorphisms in HLA genotypes are associated with various adverse drug reactions, for example, *HLA-B*5801* and allopurinol-induced SJS/TEN,[11] *HLA-B*5701* and abacavir-induced hypersensitivity,[12] *HLA-B*1502* and carbamazepine-induced SJS/TEN,[13] and *HLA-B*1592* and oxcarbazepine-induced SJS/TEN.[14]

Associations between HLA genotypes and dapsone-induced cutaneous adverse drug reactions (cADRs) have been investigated in epidemiologic studies.[15-17] We aimed to summarize and elucidate the associations between *HLA-B*1301* and dapsone-induced cADRs using systematic review and meta-analysis techniques.

Key Points

Question Is *HLA-B*1301* genotype associated with dapsone-induced cutaneous adverse reactions?

Findings In this systematic review and meta-analysis of 3 studies that included 111 patients with dapsone-induced cutaneous adverse drug reactions, 1165 dapsone-tolerant patients, and 3026 healthy controls, a statistically significant association between *HLA-B*1301* and dapsone-induced cutaneous adverse reactions was found.

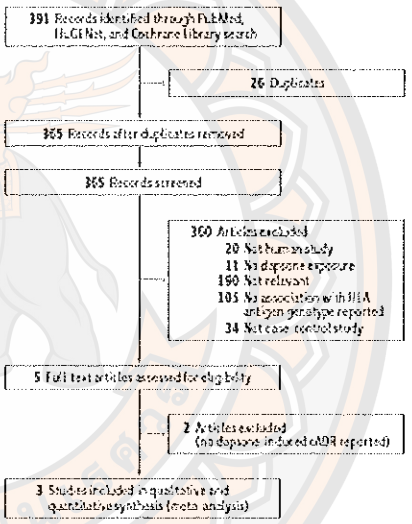
Meaning Because *HLA-B*1301* is associated with dapsone-induced cutaneous adverse reactions, genetic screening for *HLA-B*1301* before initiating dapsone therapy is warranted.

Methods

Search Strategy and Selection Criteria

A systematic literature search in PubMed, the Human Genome Epidemiology Network (HuGENet), and the Cochrane Library was performed from database inception until September 2017. Our search terms were combinations of keywords and synonyms for *HLA genotypes* and *dapsone* without language or study-design restrictions. Only human studies were included. Additional studies were retrieved from references listed in the included articles. We independently screened titles, abstracts, or both for relevance; studies deemed relevant underwent full-text article assessments for inclusion. Studies were included for case and control groups if (1) *HLA-B*1301* and dapsone-induced cADR associations were investigated; (2) all patients received dapsone before *HLA-B*1301* screening; and (3) sufficient data to calculate frequency of *HLA-B*1301* carriers were reported. If 2 or more studies shared the same population, the study with more complete data or larger sample size was included. For studies that met inclusion criteria but did not provide sufficient data for meta-analysis, we contacted corresponding authors for additional information. This additional information was not included in the present analysis.

Figure 1. PRISMA Flow Diagram of *HLA-B*1301* and Dapsone-Induced Cutaneous Adverse Drug Reactions (cADRs)



Summary of study identification, inclusion, and exclusion. HuGENet indicates Human Genome Epidemiology Network.

The PRISMA guidelines were used to abstract and assess data. We extracted data by study design; eligibility criteria, definition, and diagnostic criteria for cases and controls; patient demographics; dose and duration of dapsone exposure; HLA genotyping technique; and Hardy-Weinberg equilibrium information. The frequency of genotypes was examined by the Hardy-Weinberg equilibrium to determine whether patients from the selected studies were representative of the population.[18,19] The Newcastle-Ottawa scale was used to determine the quality of the selected studies.[20] Throughout the study, disagreements between reviewers were resolved through discussion until consensus was reached.

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Statistical Analysis

The included studies demonstrating associations between *HLA-B*1301* and dapsone-induced cADRs were characterized and summarized based on the most recent data. Overall odds ratios (ORs) with 95% CIs were calculated to determine associations between *HLA-B*1301* and dapsone-induced cADRs. All analyses were performed using the DerSimonian and Laird method under a random-effects model.[21] Analyses were also performed separately on studies using different types of control patients (eg, dapsone-tolerant or healthy controls) and different types of cADRs. Statistical heterogeneity was assessed using the *Q* statistic and I^2 tests.[22] Two-sided $P < .10$ indicated a statistically significant heterogeneity between studies. Heterogeneity I^2 values of 25%, 50%, and 75% denote low, moderate, and high heterogeneity across studies, respectively.[23] All statistical analyses were performed using R, version 3.4.0 (R Foundation for Statistical Computing).

Results

Search Strategy and Selection Criteria

Our literature search strategy and study selection process are summarized in Figure 1. The initial search of the databases identified 391 articles. After duplicate records were removed, 365 articles were screened on the basis of title, abstract, or both to determine eligibility. Three articles[15-17] met inclusion criteria. No additional articles were identified in the bibliographies of the included studies.

Study Characteristics and Quality Assessment

Characteristics of the included studies are summarized in Table 1. All of the included studies[15-17] were case-control studies. One hundred eleven unique case patients with dapsone-induced cADRs,[15-17] 1165 dapsone-tolerant controls,[15-17] and 3026 healthy controls[15-17] were included in our systematic review and meta-analysis. Mean age of included patients was 30.7 years in case patients,[15-17] 32.2 years in dapsone-tolerant control patients,[15,16] and 39.5 years in healthy controls.[15] Because some of the selected studies in this meta-analysis did not provide individual data points, SDs could not be calculated from the available information. Male patients made up 64 of 113 cases (56.6%)[15-17] (2 patients were missing from the meta-analysis; 1 each from the study by Wang et al[15] and Zhang et al[16]), 817 of 1144 dapsone-tolerant controls (71.4%),[15,16] and 53 of 100 healthy controls (53.0%).[15] The mean dose of dapsone was 94.5 mg/d (range, 2-400 mg/d).[17] Mean duration of dapsone-induced cADRs was 30.4 days (range, 1-53 days).[15,16] All included studies[15-17] were conducted in Asian populations (2 in Chinese populations[15,16] and 1 in a Thai population[17]). The studies by Wang et al[15] and Zhang et al[16] investigated the association between *HLA-B*1301* and DHS, whereas Tempark et al[17] investigated the association between *HLA-B*1301* and dapsone-induced severe cADRs. Diagnostic criteria for DHS, SJS/TEN, and DRESS for each study are summarized in Table 1. The included studies identified HLA genotypes by using polymerase chain reaction sequence-specific primers,[15] polymerase chain reaction next-generation sequencing,[16] and polymerase chain reaction sequence-specific oligonucleotide primers.[17] In the study by Zhang et al,[16] reported controls deviated significantly from the Hardy-Weinberg equilibrium ($P < 10^{-8}$). The mean score of quality assessment using the Newcastle-Ottawa scale for case-control studies was 6.3 (range, 5-7) (Table 1).

Statistical Analysis

Analysis Using Dapsone-Tolerant Control Studies

The associations between *HLA-B*1301* and dapsone-induced cADRs are summarized in Table 2. One hundred eleven patients had dapsone-induced cADRs and 1165 were dapsone tolerant. In these studies, 95 cases and 157 controls carried at least 1 *HLA-B*1301* allele. We found an association between *HLA-B*1301* and dapsone-induced cADRs (summary OR, 43.0; 95% CI, 24.0-77.2). There was no heterogeneity ($I^2 = 0\%$, $P = .38$) (Table 2 and Figure 2).

In a subgroup analysis by type of cADR, ORs were 51.7 (95% CI, 16.9-158.5; $I^2 = 46\%$; $P = .17$) in the DHS group; 54.0 (95% CI, 8.0-366.2) in the dapsone-induced severe cADRs (SJS/TEN plus DRESS) group; 40.5 (95% CI, 2.8-591.0) in the dapsone-induced SJS/TEN group; and 60.8 (95% CI, 7.4-496.0) in the dapsone-induced DRESS group (Table 2).

Analysis Using Healthy Control Studies

There were 100 patients with dapsone-induced cADRs and 3026 healthy controls. In these studies, 95 cases and 39 controls carried at least 1 *HLA-B*1301* allele. Statistically significant associations between *HLA-B*1301* and dapsone-induced cADRs were identified (Table 2).

Discussion

To our knowledge, this is the first systematic review and meta-analysis to identify the associations between *HLA-B*1301* and dapsone-induced cADRs. An association was found between the *HLA-B*1301* genotype and dapsone-induced cADRs (summary OR, 43.0; 95% CI, 24.0-77.2) (Figure 2). This statistically significant association was similar to the results of the subgroup analyses in the DHS, dapsone-induced severe cADRs (SJS/TEN plus DRESS), dapsone-induced SJS/TEN, and dapsone-induced DRESS groups (Table 2). In addition, the association between *HLA-B*1301* and dapsone-induced cADRs was found in healthy controls. In the healthy control group, there were duplicate cases in Zhang et al.[16] Therefore, summary ORs could not be calculated and this study was not included in the meta-analysis. However, the observed ORs as shown in Table 2 are still relatively high.

Allele frequency of *HLA-B*1301* (*f*) was 0 to 0.019 in European patients, 0.021 in Korean patients, and 0 to 0.015 in Japanese patients. This allele is more prevalent among Chinese (*f* = 0.009-0.211) and Southeast Asian (*f* = 0.091-0.021) populations.[26,27] Prevalence of *HLA-B*1301* is higher in Papua New Guinean (*f* = 0.283-0.132) and Australian Aboriginal (*f* = 0.132-0.270) populations.[26,27] Nonetheless, outcomes of the dapsone-induced cADRs among persons of other races/ethnicities carrying *HLA-B*1301* might be different from those in Chinese and Southeast Asian populations.

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Table 1. Characteristics of the 3 Included Studies

Source	Participant Race/Ethnicity	HLA Genotype	Type of cADR (No.)	Control (No.)	Diagnostic Criteria		NOS Rating[b]
					Cases	Controls	
Wang et al,[15] 2013	Chinese (Han Chinese, 53.6%; non-Han Chinese, 46.2%)[c]	HLA-B*1301, HLA-B*1313, HLA-C*0304	Hypersensitivity reactions (20)[c]	Tolerant control (102)	Patients who took dapsone for ≥8 wk and developed DHS; DHS was diagnosed using criteria of Richardus and Smith[14,f]	Participants who took dapsone for ≥8 wk with no episode of adverse skin reaction to a drug	6
				Healthy control (96)		NR	
Zhang et al,[15] 2013	Chinese	HLA-B*1301, HLA-C*0304	Hypersensitivity reactions (76)[c]	Tolerant control (1034)[c]; Healthy control (Shandong [523], Yunnan [470], Guangdong [951])	Patients who took dapsone and developed DHS; DHS was diagnosed using criteria of Richardus and Smith[14,f]	Patients who took dapsone ≥6 mo without DHS; NR	7
Tempark et al,[17] 2017	Thai	HLA-B*1301	SJS/TEN (4), DRESS (11)	Tolerant control (29); Healthy (305)	SJS, TEN, and DRESS were diagnosed using RegiSCAR criteria[g]; SJS was defined as skin detachment <10%; TEN, as 30% of BSA; and DRESS, by the triad of skin eruption, hematologic involvement, and internal organ involvement	Patients who took dapsone >6 mo without evidence of cADRs; NR	6

Abbreviations: BSA, body surface area; cADRs, cutaneous adverse reactions; DHS, dapsone-induced hypersensitivity; DRESS, drug rash (adverse skin reaction to a drug) along with eosinophilia and systemic symptoms; NOS, Newcastle-Ottawa scale; NR, not reported; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a] The NOS is a tool commonly used to evaluate the quality of selected studies, with a possible score of 10 (range, 0-10) based on 3 domains: selection (4 points), comparability (2 points), and exposure (4 points).[20] Greater point totals suggest higher-quality studies.

[b] Mean number from case, tolerant control, and healthy control. Because some of the selected studies in this meta-analysis did not provide individual data points, SD could not be calculated.

[c] Number of patients in the analysis.

[f] Richardus and Smith defined dapsone-induced hypersensitivity syndrome (DHS) by the following 5 criteria: (1) symptoms appear within 6 weeks after commencement of dapsone and disappear after the discontinuation of the drug; (2) symptoms cannot be ascribed to any other drug given simultaneously with dapsone; (3) symptoms are not attributable to lepra reaction; (4) no other disease likely to cause similar symptoms is diagnosed; and (5) 2 of the following signs, symptoms should be present: fever, skin eruption, lymphadenopathy, and liver pathology (hepatomegaly, jaundice, and/or abnormal liver function test results).[14]

[g] The RegiSCAR criteria defined DRESS by 2 important characteristics: multisystem involvement and frequent eosinophilia. Usually, the symptoms involve multiple systems. These include fever greater than 38°C, enlarged lymph nodes at more than 2 sites, atypical lymphocytes, extent of adverse skin reaction to a drug of more than 50% of body surface area, and/or at least 2 of the following: edema, infiltration, purpura, scaling, internal organ involvement, and resolution in more than 15 days.[21]

Table 2. Calculated ORs of the 3 Included Studies and Summary ORs Categorized by Type of Control and cADR

Source by Type of Study	Type of cADR	Race/Ethnicity	HLA-B*1301 Positive, No./Total, No. of Participants		OR (95% CI)
			Cases	Controls	
Dapsone-tolerant control studies					
Wang et al,[15] 2013	DHS	Chinese	18/20	7/102	122.1 (23.5-636.2)
Zhang et al,[15] 2013	DHS	Chinese	65/76	148/1034	35.4 (18.2-68.6)
Subtotal (I^2 = 46%; P = .17)					51.7 (16.9-158.5)
Tempark et al,[17] 2017	SJS/TEN	Thai	3/4	2/29	40.5 (2.8-591.0)
	DRESS	Thai	9/11		60.8 (7.4-495.2)
Subtotal (I^2 = NA; P = NA)					54.0 (8.0-365.2)
Summary OR (I^2 = 0%; P = .38)					43.0 (24.0-77.2)
Healthy control studies					
Wang et al,[15] 2013	DHS	Chinese	18/20	11/96	60.6 (14.2-341.1)
Zhang et al,[15] 2013	DHS	Chinese (Shandong)	65/76	35/523	62.4 (39.9-170.2)
		Chinese (Yunnan)		64/470	37.5 (18.8-74.8)
		Chinese (Guangdong)		157/951	23.9 (15.4-57.9)
Tempark et al,[17] 2017	SJS/TEN	Thai	3/4	131/305	19.6 (5.3-134.4)
	DRESS	Thai	9/11		23.4 (5.3-137.4)

Abbreviations: cADRs, cutaneous adverse reactions; DHS, dapsone-induced hypersensitivity; DRESS, drug rash (adverse skin reaction to a drug) along with eosinophilia and systemic symptoms; NA, not applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

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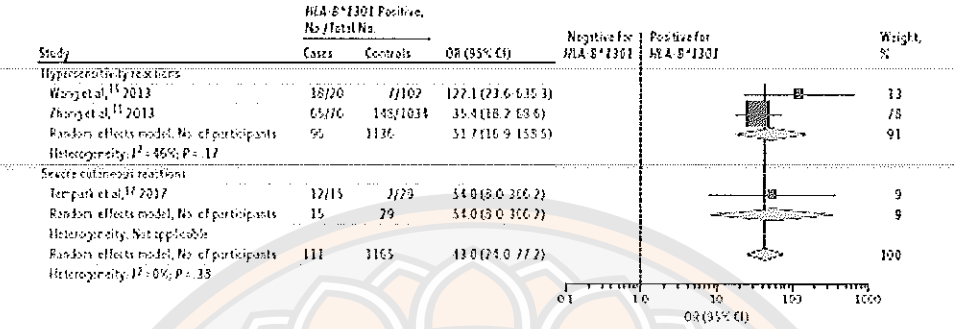
Figure 2. Associations Between *HLA-B*1301* and Dapsone-Induced Cutaneous Adverse Drug Reactions (cADRs)



Forest plot shows associations between *HLA-B*1301* and dapsone-induced cADRs using dapsone-tolerant controls. Each data marker and its size indicate a mean value and a magnitude of the data point compared with the total. Error bars indicate 95% CIs and vertical dotted line, overall estimated odds ratio (OR). Data marker size reflects the weight of the study using random-effects meta-analysis. Data were evaluated using R, version 3.4.3 (The R Foundation).

Our study demonstrated associations between *HLA-B*1301* and dapsone-induced DHS in 2 Chinese populations[15,16] and between *HLA-B*1301* and dapsone-induced severe cADRs (SJS/TEN plus DRESS) in 1 Thai population.[17] To identify any association between *HLA-B*1301* and dapsone-induced cADRs in other populations from other geographic areas, future studies are needed.

Recently, a mechanism by which *HLA-B*1301* causes DHS was proposed by Watanabe et al.[28] Dapsone specifically binds to HLA-B*1301 at the residue Ile95, a proposed binding site called "pocket F." This specific binding between dapsone and HLA-B*1301 alters the structure of the antigen-recognition site of HLA-B*1301. As a result, the structurally altered protein can recognize its ligands and this leads to the dapsone-induced cADRs.

Limitations

In this report, there were 3 studies in Asian populations (2 studies in Chinese populations and 1 study in a Thai population). Thus, more studies in more diverse populations are needed.

Conclusions

Associations between *HLA-B*1301* and dapsone-induced cADRs were identified in both dapsone-tolerant and healthy control groups. Screening for *HLA-B*1301* before initiation of dapsone therapy is warranted in Asian populations.

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REFERENCES

1. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol*. 2001;45(3):420-434.
2. Kannan G, Vasantha J, Rani NV, et al. Drug usage evaluation of dapsone. *Indian J Pharmacol*. 2000;32(4):195-200.
3. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res*. 2014;306(2):103-124.
4. Rossati SG, Guha B, Nassour EN, Chi DS, Krishnaswamy G. The dapsone hypersensitivity syndrome revisited: a potentially fatal multisystem disorder with prominent hepatopulmonary manifestations. *J Investig Med Pathol*. 2006;(1):9.
5. Vinod KV, Arun K, Dutta TK. Dapsone hypersensitivity syndrome: a rare life-threatening complication of dapsone therapy. *J Postgrad Med*. 2011;57(3):262-263.
6. Lorenz M, Worel G, Schmitt J. Hypersensitivity reactions to dapsone: a systematic review. *Acta Dermatovenerol Croat*. 2012;20(3):194-199.
7. Tian W, Shen J, Zhou M, Yan L, Zhang G. Dapsone hypersensitivity syndrome among leprosy patients in China. *Lepr Rev*. 2012;83(3):370-377.
8. Pandey B, Shrestha R, Lewis J, Hawksworth RA, Walker SL. Mortality due to dapsone hypersensitivity syndrome complicating multidrug therapy for leprosy in Nepal. *Trop Doct*. 2008;38(3):162-163.
9. Cheng WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol*. 2007;7(4):317-323.
10. Bharadwaj M, Illing P, Kostenko L. Personalized medicine for HLA-associated drug hypersensitivity reactions. *Per Med*. 2010;7(5):495-516. doi:10.2217/pme.10.46
11. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of *HLA-B*5801* allele and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *J Clin Med Genet*. 2011;17:11-18.
12. Tangamornsuksan W, Lohitnavy O, Kongkaew C, et al. Association of *HLA-B*5701* genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. *J Pharm Pharmacol*. 2012;64(1):50-61.
13. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the *HLA-B*1502* allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol*. 2013;149(9):1025-1032.
14. Chen CB, Hsiao YH, Wu T, et al; Taiwan Severe Cutaneous Adverse Reaction Consortium. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. *Neurology*. 2012;80(11):934-939.

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15. Wang H, Yan L, Zhang G, et al. Association between HLA B*13:01 and dapsone-induced hypersensitivity reactions among leprosy patients in China. *Int Arch Occup Environ Health*. 2013;86(8):861-864. doi:10.1007/s00420-012-0818-3

16. Zhang FR, Liu H, Irwanto A, et al. HLA B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med*. 2013;369(20):1920-1931. doi:10.1056/NEJMoa1309096

17. Tempark T, Satapornpong P, Rerknimitr P, et al. Dapsone-induced severe cutaneous adverse drug reactions are strongly linked to HLA B*13:01 allele in the Thai population. *Pharmacogenet Genomics*. 2016;26(10):450-456. doi:10.1097/FPC.0000000000000239

18. Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J. A method for meta-analysis of molecular association studies. *Stat Med*. 2005;24(11):1291-1306. doi:10.1002/sim.2010

19. Smits KM, Schouten JS, Smits LJ, Stelma FF, Nelemans P, Prins MH. A review on the design and reporting of studies on drug-gene interaction. *Pharmacoepidemiol Drug Saf*. 2010;19(1):1-7. doi:10.1002/pds.1858

20. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Posted 2011. Accessed September 24, 2017.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

24. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Int J Lepr Other Mycobact Dis*. 1995;63(1):1-7.

25. Roujeau JC, Allanore L, Liss Y, Mockenhaupt M. Severe cutaneous adverse reactions to drugs (SCAR): definitions, diagnostic criteria, genetic predisposition. *Zhonghua Pifuke Zazhi*. 2009;27:203-209.

26. Gonzalez-Galarza FF, Takeshita LY, Santos EJ, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res*. 2015;43(Database issue):D784-D788. doi:10.1093/nar/gku1166

27. Allele Frequency Net Database. the Allele Frequency Net Database. http://www.allelefrequencies.net. Updated January 4, 2015. Accessed September 30, 2017.

28. Watanabe H, Watanabe Y, Tashiro Y, et al. A docking model of dapsone bound to HLA B*13:01 explains the risk of dapsone hypersensitivity syndrome. *Haplomatrix*. 2014;1:e23. doi:10.7243/2052-6422-1-23

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APPENDIX B PUBLICATION OF *HLA* GENOTYPES AND OXCARZEPINE-INDUCED CUTANEOUS ADVERSE DRUGS REACTIONS

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Association Between *HLA genotypes* and Oxcarbazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review and Meta-Analysis

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ABSTRACT - PURPOSE: To systematically review and quantitatively synthesize associations between *HLA genotypes* and oxcarbazepine-induced cutaneous adverse drug reactions (OXC-cADRs), including Stevens–Johnson syndrome (SJS) and maculopapular rash. **METHODS:** Studies investigating associations between *HLA genotypes* and OXC-cADRs were systematically searched irrespective of language, in PubMed, HuGENet (Human Genome Epidemiology Network), and the Cochrane Library from their inception until January, 2017. Inclusion criteria were studies investigating associations between *HLA genotypes* and OXC-cADRs that reported sufficient data for calculating the frequency of *HLA genotype* carriers among cases and controls. Overall odds ratios (ORs) with corresponding 95%CIs were calculated using a random-effects model to determine the association between *HLA genotypes* and OXC-cADRs. **RESULTS:** The initial searches identified 91 articles, of which 6 studies met the selection criteria. The studies included 229 patients with OXC-cADRs, 251 OXC-tolerant patients, and 2,358 participants from general populations of Han Chinese, Korean, and Thai ethnicities. Associations between *HLA-B*1502* and OXC-induced SJS were found in both the general population [OR=30.2 (95%CI=3.45-264)] and in OXC-tolerant individuals [OR=26.4 (95%CI=7.98-87.6)]. An association between the *HLA-B*1502* and OXC-induced maculopapular rash was found in the general population [OR=5.67 (95%CI=2.03-15.9)] while *HLA-A*3101* also associated with OXC-induced maculopapular rash [overall OR=29.2 (95%CI=6.70-128)]. **CONCLUSIONS:** Strong associations between the HLA-B*1502 and OXC-cADRs (SJS and maculopapular rash) were found in both controls from general population and OXC-tolerant groups. There was also an association between *HLA-B*3101* and OXC-induced maculopapular rash. For patient safety, genetic screening especially for *HLA-B*1502* prior to OXC therapy at least in these closely related ethnicities is warranted. Further studies need to better define other ethnicities at risk and a wider range of MHC gene subtypes.

This article is open to **POST-PUBLICATION REVIEW.** Registered readers (see "For Readers") may **comment** by clicking on ABSTRACT on the issue's contents page.

INTRODUCTION

Oxcarbazepine (OXC) is a keto-analogue of carbamazepine (CBZ) and approved as a monotherapy or adjunctive therapy to treat partial seizures in adults and children (1). It has less severe cutaneous adverse drug reactions (cADRs) and thus a safer choice for CBZ-intolerant patients (2). OXC-cADRs vary from mild maculopapular rash to severe reactions (i.e., Stevens–Johnson syndrome/toxic epidermal necrolysis, SJS/TEN), and drug rashes with eosinophilia and systemic symptoms with eosinophilia and systemic symptoms, DRESS). However, the most common OXC-cADR is maculopapular rash (3). 25-78% of CBZ-hypersensitive patients develop a cross reaction with OXC, while 29-40% of OXC-induced hypersensitive patients cross react with CBZ (4-6).

Several studies suggested that most cADRs caused by epileptic drugs (e.g., CBZ, phenytoin, lamotrigine) are drug-specific immune responses through human leukocyte antigens (HLAs) (7, 8). HLA is a gene group encoding the major histocompatibility complex (MHC) located on chromosome 6 in humans (9, 10). MHCs are cell-surface receptors that capture and present self- and pathogen-derived peptides to T-cell receptors. The associations among MHC class I and II and OXC-

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ABBREVIATIONS: BFDE = bullous fixed drug eruption; cADRs = cutaneous adverse drug reactions; CBZ = carbamazepine; CI = confidence intervals; DRESS = drug rash with eosinophilia and systemic symptoms; HLAs = human leukocyte antigens; HuGENet = Human Genome Epidemiology Network; HWE = Hardy-Weinberg equilibrium; MHC = major histocompatibility complex; NOS = The Newcastle-Ottawa scale; OR = odds ratio; OXC = oxcarbazepine; OXC-cADRs = oxcarbazepine-induced cutaneous adverse drug reactions; PCR= polymerase chain reaction; SJS = Stevens–Johnson syndrome; TEN = Toxic epidermal necrolysis

cADRs have been studied in several epidemiological studies (11-14). However, these previous studies have shown a wide range of *HLA genotypes* (i.e., *HLA-A*3101*, *HLA-B*1502*), OXC-cADRs (i.e., maculopapular rash, SJS/TEN), and the magnitude of associations. A major limitation of the individual studies is the low incidence of OXC-cADRs. Small sample sizes among those studies may contribute observed variations. An important part of reducing cADRs is an understanding of population risks as well as *HLA genotyping* before drug treatment. Therefore, to better assess these risks, we aimed to review all relevant studies and to quantitatively synthesize the magnitude of the associations using a systematic review and meta-analysis technique.

METHODS

SEARCH STRATEGY AND SELECTION CRITERIA

PubMed, Human Genome Epidemiology Network (HuGENet) and the Cochrane Library were systematically searched from their inception until January 2017 using keyword combinations or synonyms for "*HLA genotypes*" and "oxcarbazepine" without language or study design restrictions. Only human studies were included. Additional studies were retrieved from bibliographies of the included articles. Two reviewers (WT, ML) independently screened titles and/or abstracts for relevance followed by full-text article assessments for inclusion. Studies were included if: (1) *HLA genotypes*/OXC-cADRs associations were investigated; (2) all patients received OXC before *HLA genotypes* screening, and; (3) sufficient data for calculating the frequency of *HLA genotypes* carriers were reported. When studies shared the same population, the one reporting most data and patients was selected. Where data was insufficient for meta-analysis, additional data was sought from corresponding authors.

Two reviewers (WT, ML) extracted data by study design, eligibility criteria, definition, and diagnostic criteria for cases and controls, patient demographics, dose and duration of OXC exposure, the HLA genotyping technique and Hardy-Weinberg equilibrium (HWE) information. The genotype frequencies were examined by the HWE to determine whether the patients from the selected studies were representative of the population (15, 16). Study quality used the Newcastle-Ottawa scale (NOS) comprising three domains: selection, comparability, and outcome or exposure (17). All disagreements throughout were resolved by discussion between the reviewers until consensus was made.

DATA ANALYSIS

The included studies demonstrating an association between *HLA genotypes* and OXC-cADRs were characterized and summarized based on the most recent data. The overall odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine associations between *HLA genotypes* and OXC-cADRs. All analyses were performed using the DerSimonian and Laird method under a random-effects model (18). The analyses were also performed separately on studies using different types of control (e.g., general population or OXC-tolerant control), different design, different *HLA genotypes*, and different type of OXC-cADRs.

Information regarding *HLA genotypes* was obtained from the Allele Frequency Net Database, a genetic database, and from studies reporting allele frequencies of the genes; this group was defined as a general population control. Whereas OXC-tolerant control was defined by information of *HLA genotypes* in the control group obtained from patients who received OXC without any history of cADRs.

Statistical heterogeneity was assessed via the Q-statistics and I-squared tests. P-values ≤ 0.10 indicated heterogeneity between studies (19). I-squared values of 25%, 50%, 75% denote a low, moderate, and high degree of heterogeneity across studies (20). All statistical analyses were performed using the R program (version 3.4.0) (R foundation for statistical computing, 2017).

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RESULTS

SEARCH STRATEGY AND SELECTION CRITERIA

Searching results are depicted in Figure 1. In brief, 91 articles were identified, which was whittled down to 6 studies that met our criteria (12-14, 21-23). These comprised 229 patients with OXC-cADRs, 251 OXC-tolerant patients, and 2,358 participants from general populations (12-14, 21-23). Five studies were case-controlled (12, 14, 21-23) which formed our systematic review and meta-analysis, and one was a prospective cohort (13) (Table 1).

STUDY CHARACTERISTICS AND QUALITY ASSESSMENT

Characteristics of the included studies are summarized in Table 1 and 2. Mean ages of included patients were 26.7 years in cases (12-14, 21-23) and 34.0 years (22) in controls; males made up 44.3% (58 of 131) of cases (12-14, 21-23) and 8.9% (11 of 123) of controls (22). Age and gender data were not reported where controls were from the general population. The mean dose of OXC was 315.4 mg/day (range 75-600 mg/day) (12-14, 22). The mean delay in appearance of OXC-cADRs after initiating treatment was 13.9 days (rang 1-53 days) (12-14, 22). The included studies identified *HLA genotypes* using polymerase chain reaction (PCR) as a sequence-based typing technique (12, 23), PCR sequence specific oligonucleotide primers (21) and PCR sequence specific primers (13, 14, 22). No study reported sample-size calculations before recruiting patients, nor HWE information. A mean quality assessment using NOS for case control studies (12, 14, 21-23) was 5.8 (range 5-6), whereas NOS scale of the cohort study (13) was 9 (Table 2).

SYSTEMATIC REVIEW AND META-ANALYSIS RESULTS

MHC class I and OXC-cADRs

HLA-A genotypes

The associations between *HLA-A genotypes* and OXC-cADRs of the included studies are summarized in Table 3. Two studies (21, 24) investigated associations between *HLA-A genotypes* (i.e., *HLA-A*3101 and HLA-A*3201*) and several types of OXC-cADRs (i.e., maculopapular rash, SJS, DRESS and BFDE). However, there was only sufficient data to assess the association between *HLA-A*3101* and OXC-induced maculopapular rash that could be meta-analysed. Associations between *HLA-A*3201* and OXC-induced maculopapular rash were determined by Moon et al (21) in general population control and OXC-tolerant groups. An association between *HLA-A*3201* and OXC-induced maculopapular rash was found in general population controls (overall OR=8.46, 95%CI=1.37-52.2) (Table 3). Moon et al (21) and Chen et al (23) found 8 out of 53 *HLA-A*3101* carriers in their cases general population controls, the numbers of and controls were 5 out of 579. We found an association between *HLA-A*3101* and OXC-induced maculopapular rash in the general population controls (overall OR=29.2, 95%CI=6.70-128; I^2=0.0%, p=0.45) (Figure 2). In OXC-tolerant controls, the number of *HLA-A*3101* carriers in cases was 6 out of 35 and 15 out of 156 for controls. However, there was no statistically significant association between *HLA-A*3101* and OXC-induced maculopapular rash in OXC-tolerant group (Figure 2).

HLA-B genotypes

The associations between *HLA-B genotypes* and OXC-cADRs of the included studies are summarized in Table 3. Among all of the included studies (12-14, 21-23), 42 different *HLA-B genotypes* and several types of OXC-cADRs are investigated. Associations between *HLA-B*1501*, *HLA-B*1502*, and *HLA-B*1511* and OXC-cADRs could be included into our further meta-analyses. Associations between *HLA-B*1502* and OXC-cADRs were identified.

All included studies (12-14, 21-23) investigated associations between *HLA-B*1502* and different types of OXC- types of OXC-cADRs. Two studies (14, 23) investigated associations between *HLA-B*1502* and OXC-induced SJS in general population controls and OXC-tolerant group. In the general population groups, there were 4 *HLA-B*1502* carriers out of 5 cases and 14 out of 137 for controls. The overall OR was 30.2 (95%CI=3.45-264; I^2=0.0%, p=0.80) (Figure 3A and Table 3). In OXC-tolerant controls, there were 13 *HLA-B*1502* carriers out of 19 cases and 8 out of 109 for controls. The overall OR was 26.4 (95%CI=7.98-87.6; I^2=0.0%, p=0.64) (Figure 3A and Table 3).

All included studies (12-14, 21-23) investigated associations between *HLA-B*1502* and OXC-induced maculopapular rash. However, only case control studies were meta-analysed. In the case-control studies (12, 14, 21-23), the incidence of *HLA-B*1502* carriers in cases, general population control, and OXC-tolerant groups were 6 out of 67, 51 out of 1,930, and 15 out of 216 respectively. In general population controls, the

overall OR was 5.67 (95%CI=2.03-15.9; I^2=0.0%, p=0.76) (Figure 3B and Table 3).

In addition, we combined numbers of OXC-induced maculopapular rash and OXC-induced SJS events in to further investigate their associations between *HLA-B*1502* and OXC-induced maculopapular rash and SJS. In general population controls only, *HLA-B*1502* was associated with OXC-induced maculopapular rash and SJS; overall OR was 7.15 (95%CI=2.64-19.4; I^2=0.0%, p=0.50) (Figure 3C and Table 3).

Only Moon et al (21) studied the *HLA-B*4002* genotype and OXC-induced maculopapular rash by comparing cases with either the general population [OR=4.04 (95%CI=1.83-8.90)] or with their OXC-tolerant group [OR=4.33 (95%CI=1.36-13.8)] (Table 3).

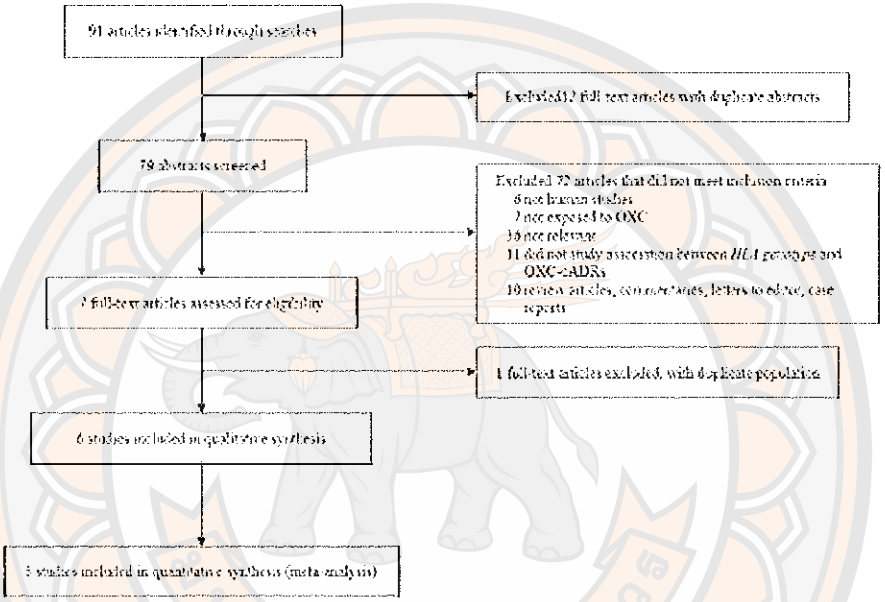

Figure 1 Summary of study identification, inclusion, and exclusion

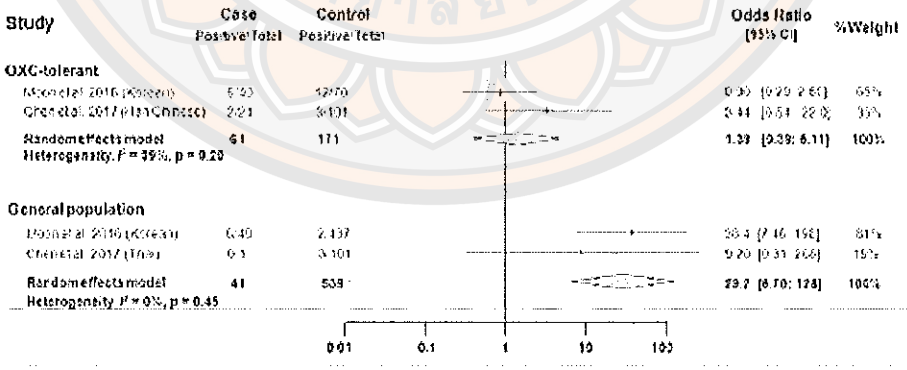

Figure 2 Forest plot of the associations between *HLA-A*3101* and OXC-induced maculopapular rash

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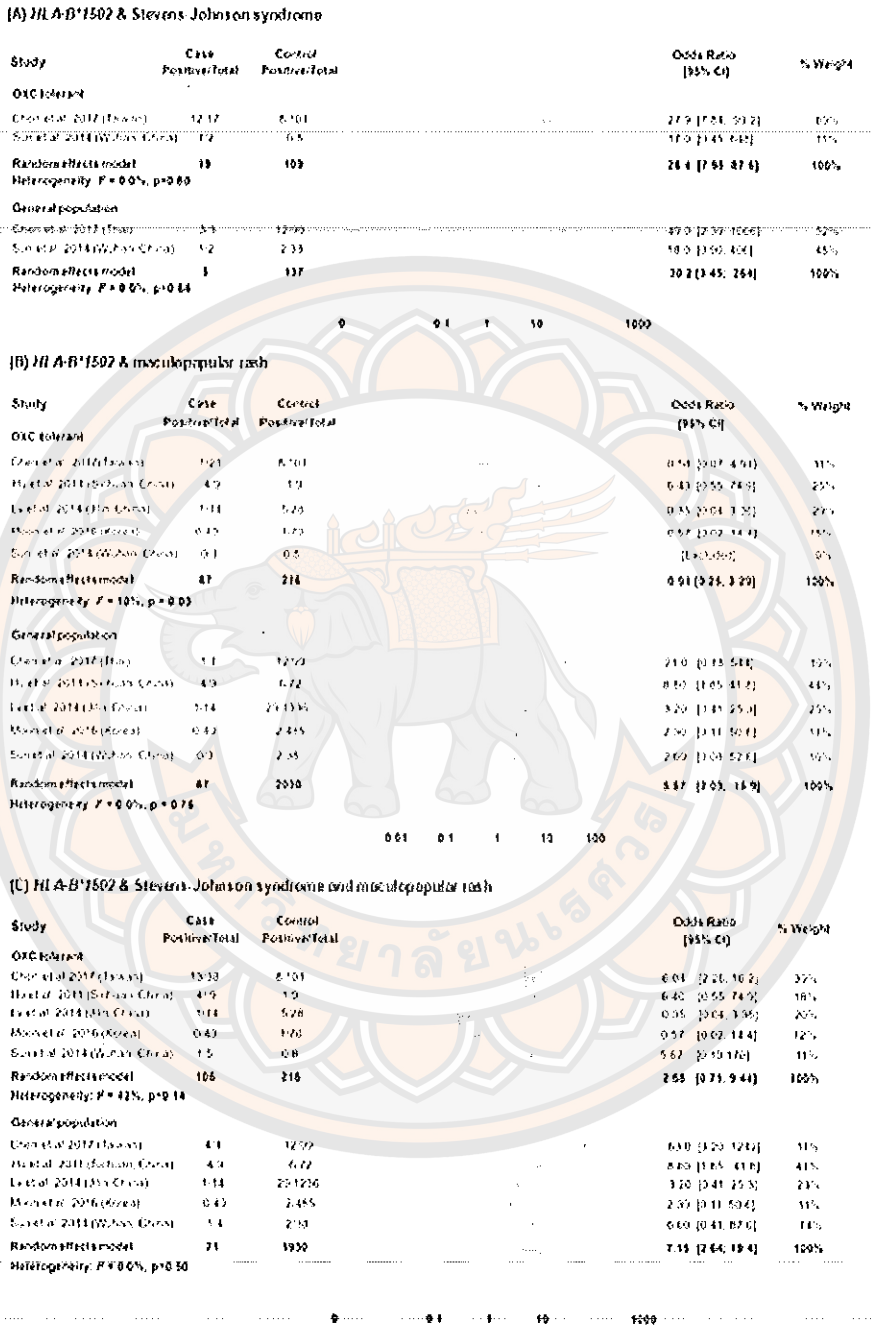

Figure 3 Forest plots of the associations between *HLA-B*1502* and OXC-induced Stevens-Johnson syndrome (A), the associations between *HLA-B*1502* and OXC-induced maculopapular rash (B), and, the associations between *HLA-B*1502* and OXC-induced Stevens-Johnson syndrome and maculopapular rash (C).

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MHC class II and OXC-cADRs

The associations between MHC class II and OXC-cADRs are summarized in Table 3. Associations between *HLA-DQB1*0501, HLA-DQB1*0503, HLA-DRB1*0403, HLA-DRB1*0406, and HLA-DRB1*1405* and with OXC-induced maculopapular rash in a Korean population were determined by Moon et al (21). *HLA-DRB1*0403* was associated with OXC-induced maculopapular rash by comparing cases with either the general population or the OXC-tolerant group as controls; OR=3.11 (95%CI=1.27-7.59) and 14.64 (95%CI=1.73-124), respectively (Table 3).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis study to identify the associations between *HLA genotypes* and OXC-cADRs. In our study, 49 different *HLA genotypes* were identified as risks of OXC-cADRs but meta-analysis could be applied to only 4 of these (i.e., *HLA-A*3101, HLA-B*1501, HLA-B*1502*, and *HLA-B*1511*). Of these *HLA-A*3101* and *HLA-B*1502* were associated with OXC-cADRs (Figure 2-3). All of the other *HLA genotypes* and OXC-cADRs are summarized in Table 3.

Notably, we found associations between *HLA-B*1502* and OXC-induced SJS in both general population control and OXC-tolerant groups. The ORs were close to those of the general population and OXC-tolerant control [OR=30.2 (95%CI=3.45-264) and OR=26.4 (95%CI=7.98-87.6), respectively] (Figure 3A). Nonetheless, due to limited number of studies, more studies investigating associations between *HLA-B*1502* and OXC-induced SJS/TEN are needed. In addition, *HLA-B*1502* was associated with OXC-induced maculopapular rash in general population controls (OR=5.67, 95%CI=2.03-15.9) (Figure 3B). To further investigate the associations between *HLA-B*1502* and OXC-induced maculopapular rash and SJS, we combined OXC-induced maculopapular rash groups with OXC-induced SJS groups. Then, *HLA-B*1502* was associated with the OXC-induced maculopapular rash/SJS group, comparing the general population [OR=7.15 (95%CI=2.64-19.4)] (Figure 3C). Nonetheless, the association between *HLA-A*3101* and OXC-induced maculopapular rash was observed in general population controls [OR=29.2 (95% CI=6.70-128)] (Figure 2).

Other OXC-induced pathologies such as TEN are not well studied and, to our knowledge, are confined to studies where SJS and TEN data were pooled (7, 11, 25). Thus, based on current findings and the previous studies, subjects harboring the allele might develop TEN when given OXC.

All of the included studies were from Han-Chinese, Thai and Korean populations (12-14, 21-23). Whether these associations with OXC-cADRs are more widespread need large-scale studies in more ethnically diverse populations.

We found two studies (21, 23) that found associations between *HLA-A*3101* and OXC-induced cADRs while for CBZ-induced cADRs (i.e., maculopapular rash) other ethicities including Caucasian and Japanese are susceptible (26-30). Furthermore, associations between *HLA-A*3101* and CBZ-induced SJS/TEN were also reported in some studies (26, 30) which suggests that *HLA-A*3101* could also induce OXC-cADRs. Thus in further studies that we suggest using wider ethnic groups, a wider range of MHC genes should be included.

Recently, 3D molecular coupling models of HLA protein molecules and carbamazepine, oxcarbazepine and abacavir were developed (31, 32). These models shed an understanding of how HLA molecules binds specifically to their ligands and potentially causes those adverse drug reactions (i.e. Steven-Johnson syndrome, toxic epidermal necrolysis, DRESS) (31). Despite the structural similarities of OXC and CBZ and their reported cross-reactivity, OXC does not share the HLA-related risk factors with CBZ-induced SJS/TEN which are 30-40 folds more than for OXC in Han Chinese (24). In addition, some patients carrying *HLA-B*1502* with a history of CBZ-induced SJS could tolerate OXC (23). To understand the biological basis of this, the mechanism of the cross reactivity needs further studies.

CONCLUSION

Strong associations between the *HLA-B*1502* and OXC-cADRs (SJS and maculopapular rash) were found in both controls from cases using either control from either the general population or and OXC-tolerant groups. In general population controls, OXC-induced maculopapular rash was associated with *HLA-A*3101*. These strong links were detected in Korean, Han-Chinese and Thai ethnicities. Therefore, a genetic screening in these ethnicities should precede an OXC treatment. For other populations, genetic screening of *HLA-B*1502* prior to OXC therapy may be warranted. However, screening for a wider range of both MHC genotype and ethnicities should be undertaken.

REFERENCES

1. Kalis M, Huff N. Oxcarbazepine, an antiepileptic agent. Clin Ther. 2001 May;23(5):680-700.
2. McAuley J, Biederman T, Smith J, Moore J. Newer therapies in the drug treatment of epilepsy. Ann Pharmacother. 2002 Jan;36(1):119-29.
3. Yang C, Dao R, Lee T, Lu C, Yang C, Hung S, et al. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology. 2011 Dec 6;77(23):2025-33.
4. Alvestad S, Lydersen S, Brodtkorb E. Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. Epilepsy Res. 2008 Aug;80(2-3):194-200.
5. Hirsch L, Arif H, Nahm E, Buchsbaum R, Resor SJ, Bazil C. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology. 2008 Nov 4;71(19):1527-34.
6. Wang X, Lang S, Shi X, Tian H, Wang R, Yang F. Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. Seizure. 2010 Nov;19(9):562-6.
7. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship Between the HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. JAMA Dermatol 2013 Sep 1;149(9):1025-32.
8. Li X, Yu K, Mei S, Huo J, Wang J, Zhu Y, et al. HLA-B*1502 increases the risk of phenytoin or lamotrigine induced Stevens-Johnson Syndrome/toxic epidermal necrolysis: evidence from a meta-analysis of nine case-control studies. Drug Res (Stuttg). 2015 Feb;65(2):107-11.
9. Chung W, Hung S, Chen Y. Human leukocyte antigens and drug hypersensitivity. Current Opinion in Allergy & Clinical Immunology. 2007;7(4):317-23.
10. Bharadwaj M, Illing P, Kosterko L. Personalized medicine for HLA-associated drug-hypersensitivity reactions. Personalized Medicine. 2010;7(5):495-516.
11. Hung S, 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 Mar;11(3):349-56.
12. Hu F, Wu X, An D, Yan B, Stefan H, Zhou D. Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population. Seizure. 2011 Mar;20(2):160-2.
13. He N, Min FL, Shi YW, Guo J, Liu XR, Li BM, et al. Cutaneous reactions induced by oxcarbazepine in Southern Han Chinese: Incidence, features, risk factors and relation to HLA-B alleles. Seizure. 2012 Oct;21(8):614-8.
14. 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 Feb;34(1):146-50.
15. Smits K, Schouten J, Smits L, Stelma F, Neleman P, Prins M. A review on the design and reporting of studies on drug-gene interaction. J Clin Epidemiol. 2005;58(7):651-4.
16. Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J. A method formeta-analysis of molecular association studies. Stat Med. 2005;24(9):1291-306.
17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2011; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
19. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
20. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.
21. 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 Nov;57(11):1879-86.
22. Lv Y, Min FL, Liao WP, He N, Zeng T, Ma DH, et al. The association between oxcarbazepine-induced maculopapular eruption and HLA-B alleles in a northern Han Chinese population. BMC Neurol. 2013 Jul 8;13:75.
23. Chen C, Hsiao YH, Wu T, Hsih MS, Tassaneeyakul W, Jorns TP, et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology. 2017 Jan 3;88(1):78-86.
24. Chen YC, Chu CY, Hsiao CH. Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with HLA-B*1502 genotype. J Eur Acad Dermatol Venereol. 2009 Jun;23(6):702-3.
25. Nguyen D, Chu HC, Nguyen DV, Phan MH, Craig T, Baumgart K, et al. HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. Asia Pac Allergy. 2015 Apr;5(2):68-77.
26. Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, Chang PY, et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J. 2014 Jun;14(3):281-8.
27. 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. Hum Mol Genet. 2011 Mar 1;20(5):1034-41.
28. Hung S, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006 Apr;16(4):297-306.
29. Amstutz U, Ross CJ, Castro-Pastrana LI, Rieder MJ, Shear NH, Hayden MR, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Ther. 2013 Jul;94(1):142-9.
30. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011 Mar 24;364(12):1134-43.
31. Teh LK, Selvaraj M, Bannur Z, Ismail MI, Rafia H, Law WC, et al. Coupling Genotyping and Computational Modeling in Prediction of Anti-epileptic Drugs that cause Stevens Johnson Syndrome and Toxic Epidermal Necrolysis for Carrier of HLA-B*15:02. J Pharm Pharm Sci. 2016;19(1):147-60.
32. Illing P, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012 Jun 28;486(7404):554-8.

APPENDIX C MANUSCRIPT OF *HLA-B*5901* AND METHAZOLAMIDE-INDUCED STEVENS–JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Association between *HLA-B*5901* and methazolamide-induced Stevens–Johnson syndrome/toxic epidermal necrolysis: A systematic review and meta-analysis

Running title: ***HLA-B*5901*** **and methazolamide-induced SJS/TEN**

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Acquisition, analysis, and interpretation of data: Ms. Tangamornsuksan and Dr. Lohitnavy

Drafting of the manuscript: Ms. Tangamornsuksan and Dr. Lohitnavy

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Abstracts

Methazolamide-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are life-threatening adverse drug reactions. Based on previous studies, *HLA genotypes* may play an important role in methazolamide-induced SJS/TEN. Therefore, to identify the associations between *HLA genotypes* and methazolamide-induced cutaneous adverse drug reactions (cADRs) (i.e. SJS/TEN and hypersensitivity syndrome), meta-analyses were performed. Two studies (one study in Korean and another in Han Chinese) met the inclusion criteria. The studies included 13 patients with methazolamide-induced SJS/TEN, 30 methazolamide-tolerant and 768 population controls. The associations between *HLA-B*5901*, *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were identified in methazolamide-tolerant and population controls. Summary ORs were 305.0 (95%CI=11.3-8,259.4) in methazolamide-tolerant and 715.3 (95%CI=83.1-6,158.5) in population control. Addition, statistically significant associations between the *HLA-Cw*0102* and methazolamide-induced SJS/TEN were found in methazolamide-tolerant (OR=12.1; 95%CI=1.3-111.7) and population control (OR=17.5; 95%CI=3.2-96.6). Since *HLA-B*5901* and *HLA-B*5901-Cw*0102* haplotype are associated with methazolamide-induced SJS/TEN, genetic screening prior to methazolamide therapy in Asian populations is warranted.

Keywords: *HLA genotypes*, *HLA-B*5901*, *HLA-Cw*0102*, *HLA-B*5901-Cw*0102* haplotype, human leukocyte antigens, methazolamide-induced SJS/TEN, SJS/TEN, Stevens–Johnson syndrome, toxic epidermal necrolysis, meta-analysis, systematic review

Abbreviations: cADRs = cutaneous adverse reactions; CI = confidence intervals; HLAs = human leukocyte antigens; HuGENet = Human Genome Epidemiology Network; HWE = Hardy-Weinberg equilibrium; NOS = The Newcastle-Ottawa scale; OR = odds ratio; PCR= polymerase chain reaction; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis

Introduction

Methazolamide is a carbonic anhydrase inhibitor. The drug is indicated in the treatment of increased intraocular pressure in chronic open-angled glaucoma and secondary glaucoma [1, 2]. Structurally, methazolamide has a sulfone group in its chemical structure, similarly to those of sulfonamide drugs (e.g. sulfamethoxazole, sulfisoxazole) [1].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening hypersensitivity reactions [3-5]. Both SJS and TEN are characterized by blisters arising on purple macules on the lips, eyes, mouth, genitals and airways [4, 5]. The skin detachment percentage differentiates SJS (less than 10%), SJS/TEN overlap (between 10%-30%) and TEN (more than 30%) [6]. Despite relatively low incidence of SJS (1.2-6 cases per million persons per year) [7-9] and TEN (0.4-1.2 cases per million persons per year) [7-10] mortality rates of SJS and TEN are relatively high (4.8% for SJS, 19.4% for SJS /TEN overlap and 14.8% for TEN).[4] Medication (e.g. sulfonamides, antiepileptic drugs, allopurinol) and genetic predisposition play a significant role in SJS/TEN.[11, 12] Human leukocyte antigen (HLA) genotypes are a family of genes involving immune reactions. Associations between *HLA genotypes* and sulfonamides-induced SJS/TEN are well-established [11, 13, 14]. *HLA genotypes* are the most polymorphic gene cluster in the human genome [10, 15]. Specific polymorphisms in *HLA genotypes* are associated with various adverse drug reactions, for example the associations between *HLA-B*5801* and allopurinol-induced SJS/TEN [16], *HLA-B*5701* and abacavir-induced hypersensitivity [17], *HLA-B*1502* and carbamazepine-induced SJS/TEN [18], *HLA-B*1502* and oxcarbazepine-induced SJS/TEN [19].

Since methazolamide and sulfonamide drugs share a striking similarity in their chemical structures, it is possible that exposure to methazolamide may be able to induce SJS/TEN [20-24]. There are several reports regarding use of methazolamide and *HLA genotypes* may be associated with increased risks in developing SJS/TEN [14, 25-32]. Therefore, we aimed to systematically review and to quantitatively synthesize associations between methazolamide-induced cADRs and certain *HLA genotypes* using a systematic review and meta-analysis technique.

Methods

Search Strategy and Selection Criteria

A systematic literature search in PubMed, Human Genome Epidemiology Network (HuGENet) and Cochrane Library was performed from inception until December 2017. The combinations of keywords or synonyms for "*HLA genotypes*" and "methazolamide" were used without language or study design restrictions for search

terms. Only human studies were included. Additional studies were retrieved from bibliographies of the included articles. Two reviewers (WT, ML) independently screened titles and/or abstracts for relevance followed by full-text article assessments for inclusion. Studies were included for case and control groups if: (1) *HLA genotypes* and methazolamide-induced cADRs associations were investigated; (2) all patients received methazolamide before *HLA genotypes* screening, and; (3) sufficient data for calculating frequency of *HLA genotypes* carriers were reported. If two or more studies shared the same population, a study with a more complete data or a larger sample size would be included. Any disagreements were discussed until consensus between the 2 reviewers could be reached. For the studies met the inclusion criteria but did not provide sufficient data for meta-analysis, corresponding authors of the selected papers would be contacted and requested for additional information. In addition, for all of the selected studies, reference lists were examined for additional relevant studies.

Two reviewers (WT, ML) extracted data by study design, eligibility criteria, definition, and diagnostic criteria for cases and control, patient demographics, dose and duration of methazolamide exposure, the HLA genotyping technique and Hardy-Weinberg equilibrium (HWE) information. The frequency of genotypes were examined by the HWE to determine whether the patients from the selected studies were representative of the population [33, 34]. For the quality of the selected studies, the Newcastle-Ottawa scale (NOS) was employed [35]. All disagreements throughout were resolved through discussion until consensus could be made.

Data Analysis

The included studies demonstrating the associations between *HLA genotypes* and methazolamide-induced cADRs associations were characterized and summarized based on the most recent data. The overall odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine associations between *HLA genotypes* and methazolamide-induced cADRs. All analyses were performed using the DerSimonian and Laird method under a random-effects model [36]. The analyses were also performed separately on the studies using different types of control (e.g., methazolamide-tolerant controls or general population controls), different type of *HLA genotypes* and different type of cADRs. Statistical heterogeneity was assessed using the Q-statistics and I-squared tests [37]. P-values less than or equal to 0.10 indicated a statistically significant heterogeneity between studies. I-squared values of 25%, 50% and 75% denote a low, moderate, and high of heterogeneity across studies, respectively [38]. All statistical analyses were performed using the R Program (version 3.4.3) (R Foundation for Statistical Computing 2017).

Results

Search Strategy and Selection Criteria

Our literature search strategy and study selection process are depicted in Fig. 1. The initial search from the databases identified 92 articles. After duplicate records were removed, 87 articles were first screened on the basis of title and/or abstract to determine the eligibility. Two articles [30, 32] from Korean and Han Chinese population met the inclusion criteria. No additional articles were identified in the bibliographies of the included studies.

Study Characteristics and Quality Assessment

Characteristics of the included studies are summarized in Table 1. In total of 13 patients with methazolamide-induced SJS/TEN [30, 32], 30 methazolamide-tolerant [32] and 768 general population controls [30, 32] were included in our systematic review and meta-analysis. Both of the included studies were case-control studies examining associations between *HLA genotypes* and methazolamide-induced SJS/TEN [30, 32]. TEN was developed in 10 out of 13 (76.9%) patients with methazolamide-induced SJS/TEN group [30, 32]. Mean ages of the patients were 46 years [30, 32] and 57.6 years [32] in cases and in methazolamide-tolerant controls, respectively. Male subjects made up of 61.5% (8 of 13) of cases [30, 32] and 36.7% (11 of 30) methazolamide-tolerant controls [32]. The range dose of methazolamide was 50-150 mg/day [30, 32]. Mean duration of methazolamide-induced SJS/TEN was 16.5 days (rang 1-58 days) [30, 32]. Both of the included studies conducted in Asian population [30, 32] (1 study in Korean population [30] and another study in Han Chinese population [32]). All of the included studies investigated the associations between *HLA-B*5901*, *HLA-Cw*0102*, the haplotype and methazolamide-induced SJS/TEN [30, 32]. Nonetheless, Kim, et al [30] also investigated the associations between *HLA-A*2402* and methazolamide-induced SJS/TEN. Diagnostic criteria for SJS/TEN of the two studies is summarized in Table 1. Yang et al. [32] used polymerase chain reaction sequencing of specific oligonucleotide (PCR-SSO) to identify *HLA genotypes* whereas, Kim, et al. [30] used a direct DNA sequence analysis technique. HWE information were not reported in neither one of the included studies [30, 32]. A mean value of the quality assessment using the NOS of case-control studies was 6.5 (range 6-7) (Table 1).

Data Analysis

Associations between *HLA-B*5901* and methazolamide-induced SJS/TEN

We found strong associations between *HLA-B*5901* and methazolamide-induced SJS/TEN in both methazolamide-tolerant and general population controls. The numbers of patients carrying with at least one

148 allele of *HLA-B*5901* were 7 out of 8 in cases and none out of 30 in methazolamide-tolerant controls [32]. In
149 methazolamide-tolerant controls group, the overall OR was 305.0 (95%CI=11.3-8,259.4) (Fig. 2A and Table 2).
150 The numbers of patients carrying with at least one allele of *HLA-B*5901* were 12 out of 13 in cases and 21 out
151 of 768 in general population controls [30, 32]. In general population controls group, the overall OR was 715.3
152 (95%CI=83.1-6,158.5). There was no heterogeneity (I^2=9.3%, p=0.29) (Fig. 2A and Table 2).
153 **Associations between *HLA-Cw*0102* and methazolamide-induced SJS/TEN**
154 Associations between *HLA-Cw*0102* and methazolamide-induced SJS/TEN were found in both methazolamide-
155 tolerant and general population controls. The numbers of patients carrying with at least one allele of *HLA-*
156 *Cw*0102* were 7 out of 8 in cases and 11 of 30 in methazolamide-tolerant controls [32]. In methazolamide-
157 tolerant controls group, the overall OR was 12.1 (95%CI=1.3-111.7) (Fig. 2B and Table 2). The numbers of
158 patients carrying with at least one allele of *HLA-Cw*0102* were 12 out of 13 in cases and 108 out of 768 in
159 general population controls [30, 32]. In general population controls group, the overall OR was 17.5
160 (95%CI=3.2-96.6). There was no heterogeneity (I^2=0.0%, p=0.85) (Fig. 2B and Table 2).
161 **Associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN**
162 Strong associations between *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN were also
163 found in both methazolamide-tolerant and general population controls. The numbers of patients carrying this
164 haplotype were 7 out of 8 in cases and none out of 30 in methazolamide-tolerant controls [32]. In
165 methazolamide-tolerant controls group, the overall OR was 305.0 (95%CI=11.3-8,259.4) (Fig. 2C and Table 2).
166 The numbers of patients carrying this haplotype were 12 out of 13 in cases and 21 out of 768 general population
167 controls [30, 32]. In general population controls group, the overall OR was 715.3 (95%CI=83.1-6,158.5). There
168 was no heterogeneity (I^2=9.3%, p=0.29) (Fig. 2C and Table 2).
169 **Discussion**
170 To our knowledge, this is the first systematic review and meta-analysis study to identify the associations
171 between *HLA-B*5901* and methazolamide-induced SJS/TEN. Strong associations between *HLA-B*5901* and
172 methazolamide-induced SJS/TEN with summary ORs of 305.0 (95%CI=11.3-8,259.4) and 715.3 (95%CI=83.1-
173 6,158.5) in methazolamide-tolerant and general population controls, respectively. (Fig. 2A, and Table 2). These
174 statistically significant associations were as high as when compared to the results of the associations between
175 *HLA-B*5901-Cw*0102* haplotype and methazolamide-induced SJS/TEN in both methazolamide-tolerant and
176 general population controls (Fig. 2C, and Table 2). In addition, the association between the *HLA-Cw*0102* and
177 methazolamide-induced SJS/TEN was also identified in methazolamide-tolerant and general population

178 controls. Summary ORs were 12.1 (95%CI=1.3-111.7) and 17.5 (95%CI=3.2-96.6) in methazolamide-tolerant
179 and general population controls, respectively. (Fig. 2B, and Table 2).
180 Allele frequency of *HLA-B*5901* (*f*) in Japanese, Korean and Han-Chinese were 0.0090-0.0204, 0.0185-0.0204
181 and 0-0.0010, respectively [39]. *HLA-B*5901-Cw*0102* haplotype is commonly detected in Japanese and
182 Korean population. *HLA-B*5901-Cw*0102* haplotype frequency in general Japanese population were 1.60%
183 whereas, *HLA-A*2402-B*5901-Cw*0102* were 1.70% in general Korean population [40].
184 In our study, the associations between *HLA-B*5901*, *HLA-Cw*0102*, *HLA-B*5901-Cw*0102* haplotype and
185 methazolamide-induced SJS/TEN in Korean and Han-Chinese population were demonstrated [30, 32].
186 However, the first case report of methazolamide-induced SJS were reported in two Japanese-American descents
187 [21]. Several case reports of methazolamide-induced SJS/TEN in patients who carried *HLA-B*59* and *HLA-*
188 *B*5901* were reported in Japanese, Korean and Han-Chinese population [26-29].
189 Interestingly, carbonic anhydrase inhibitor drugs (i.e., acetazolamide, brinzolamide and dorzolamide) -induced
190 SJS/TEN were also reported also in Japanese, Korean and Han-Chinese population [23, 41-43]. However, HLA
191 genotyping was not investigated in these studies. Since all of the drugs in this class harbor a sulfone group in
192 their chemical structures, like sulfonamides, it is possible that other drugs in this group may be able to cause
193 cADRs including SJS/TEN. Thus, more studies investigating associations between *HLA genotypes* and carbonic
194 anhydrase inhibitor drugs-induced cADRs are needed. Since the risk of cADRs of the carbonic anhydrase
195 inhibitors is relatively high, particularly among Asian populations, the drugs should be used with cautions and
196 patients should be informed about these adverse drug reactions prior to the start of their drug treatment.
197
198 **Conflict of Interest**
199 The authors declared no conflicted of interest.

References

1. Maren TH, Haywood JR, Chapman SK, Zimmerman TJ. The pharmacology of methazolamide in relation to the treatment of glaucoma. Investigative ophthalmology & visual science. 1977;16(8):730-42.
2. PubChem Compound Database [Internet]. National Center for Biotechnology Information. [cited December 21, 2017]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/4106.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. The New England journal of medicine. 1994;331(19):1272-85.
4. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. 2017.
5. Ergen EN, Hughey LC. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. JAMA Dermatol. 2017;153(12):1344.
6. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209(2):123-9.
7. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Update. American journal of clinical dermatology. 2015;16(6):475-93.
8. Oliveira A, Sanches M, Selores M. Stevens-Johnson syndrome and toxic epidermal necrolysis. Acta medica portuguesa. 2011;24 Suppl 4:995-1002.
9. Arantes LB, Reis CS, Novaes AG, Carvalho MR, Gottems LBD, Novaes M. Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiological and clinical outcomes analysis in public hospitals. Anais brasileiros de dermatologia. 2017;92(5):661-7.
10. Bharadwaj M, Illing P, Kostenko L. Personalized medicine for HLA-associated drug-hypersensitivity reactions. Personalized Medicine. 2010;7(5):495-516.
11. 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. Pharmacogenetics and genomics. 2008;18(2):99-107.
12. Illing PT, Purcell AW, McCluskey J. The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions. Immunogenetics. 2017;69(8-9):617-30.
13. Kongpan T, Maharirimongkol S, Konyoung P, Kanjanawart S, Chumworathayi P, Wichukchinda N, et al. Candidate HLA genes for prediction of co-trimoxazole-induced severe cutaneous reactions. Pharmacogenetics and genomics. 2015;25(8):402-11.

14. Rufini S, Ciccacci C, Politi C, Giardina E, Novelli G, Borgiani P. Stevens-Johnson syndrome and toxic epidermal necrolysis: an update on pharmacogenetics studies in drug-induced severe skin reaction. Pharmacogenomics. 2015;16(17):1989-2002.

15. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. Current opinion in allergy and clinical immunology. 2007;7(4):317-23.

16. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC medical genetics. 2011;12:118.

17. Tangamornsuksan W, Lohitnavy O, Kongkaew C, Chaiyakunapruk N, Reisfeld B, Scholfield NC, et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2015;18(1):68-76.

18. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA dermatology. 2013;149(9):1025-32.

19. Chen CB, Hsiao YH, Wu T, Hsih MS, Tassaneeyakul W, Jorns TP, et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology. 2017;88(1):78-86.

20. Rijal JP, Pompa T, Giri S, Bhatt VR. A case of toxic epidermal necrolysis caused by trimethoprim-sulfamethoxazole. BMJ case reports. 2014;2014.

21. Flach AJ, Smith RE, Fraunfelder FT. Stevens-Johnson syndrome associated with methazolamide treatment reported in two Japanese-American women. Ophthalmology. 1995;102(11):1677-80.

22. Cotter JB. Methazolamide-induced Stevens-Johnson syndrome: a warning! Archives of ophthalmology (Chicago, Ill : 1960). 1998;116(1):117.

23. Her Y, Kil MS, Park JH, Kim CW, Kim SS. Stevens-Johnson syndrome induced by acetazolamide. The Journal of dermatology. 2011;38(3):272-5.

24. Carroll OM, Bryan PA, Robinson RJ. Stevens-Johnson syndrome associated with long-acting sulfonamides. Jama. 1966;195(8):691-3.

25. Xu Y, Wu M, Sheng F, Sun Q. Methazolamide-induced toxic epidermal necrolysis in a Chinese woman with HLA-B5901. Indian journal of ophthalmology. 2015;63(7):623-4.

258 26. Shu C, Shu D, Tie D, Yu M, Zhang R, Wang T, et al. Toxic epidermal necrolysis induced by
259 methazolamide in a Chinese-Korean man carrying HLA-B*59:01. International journal of dermatology.
260 2015;54(11):1242-5.
261 27. Shirato S, Kagaya F, Suzuki Y, Joukou S. Stevens-Johnson syndrome induced by methazolamide
262 treatment. Archives of ophthalmology (Chicago, Ill : 1960). 1997;115(4):550-3.
263 28. Moon JI, Sao JH, Park CK. Association of HLA type with Stevens - Johnson syndrome induced by
264 methazolamide treatment. . J Korean Ophthalmol Soc 2000;41:2241.
265 29. Sung KH, Jeong Y, Choi HU, Lee SK. Two cases of HLA-B59(+) Stevens-Johnson syndrome-toxic
266 epidermal necrolysis associated with methazolamide treatment. Korean J Dermatol 2005;43:561-3.
267 30. Kim SH, Kim M, Lee KW, Kim SH, Kang HR, Park HW, et al. HLA-B*5901 is strongly associated
268 with methazolamide-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Pharmacogenomics.
269 2010;11(6):879-84.
270 31. Yang F, Yang Y, Zhu Q, Chen SA, Fu X, Yan S, et al. Research on susceptible genes and
271 immunological pathogenesis of cutaneous adverse drug reactions in Chinese Hans. The journal of investigative
272 dermatology Symposium proceedings. 2015;17(1):29-31.
273 32. Yang F, Xuan J, Chen J, Zhong H, Luo H, Zhou P, et al. HLA-B*59:01: a marker for Stevens-Johnson
274 syndrome/toxic epidermal necrolysis caused by methazolamide in Han Chinese. The pharmacogenomics
275 journal. 2016;16(1):83-7.
276 33. Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J. A method for meta-analysis of molecular
277 association studies. Stat Med. 2005;24(9):1291-306.
278 34. Smits K, Schouten J, Smits L, Stelma F, Nelemans P, Prins M. A review on the design and reporting of
279 studies on drug-gene interaction. J Clin Epidemiol. 2005;58(7):651-4.
280 35. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale
281 (NOS) for assessing the quality of nonrandomized studies in meta-analyses 2011 [Available from:
282 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
283 36. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
284 37. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
285 38. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ. 2003
286 Sep 6;327(7414):557-60.

287 39. The Allele Frequency Net Database [Internet]. 2015 [cited December 20, 2017]. Available from:
288 http://www.allelefrequencies.net.
289 40. Gonzalez-Galarza FF, Takeshita LY, Santos EJ, Kempson F, Maia MH, da Silva AL, et al. Allele
290 frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction
291 associations. Nucleic acids research. 2015;43(Database issue):D784-8.
292 41. Kim JW, Shin SY. Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome Caused by Topical
293 Ophthalmic Use of Dorzolamid. Korean J Dermatol. 2009;27(3):317-21.
294 42. Lee JH LS, Kim YH. A case of Stevens-Johnson syndrome after acetazolamide use. J Korean
295 Ophthalmol Soc. 1998;39(1):216-20
296 43. Chun JS, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Toxic epidermal necrolysis induced by the
297 topical carbonic anhydrase inhibitors brinzolamide and dorzolamide. Annals of dermatology. 2008;20(4):260-2.
298 44. Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -
299 DQB1 genes in the Korean population. Tissue antigens. 2005;65(5):437-47.
300

301 **Legends to figures**

302 **Fig. 1.** PRISMA flow diagram of *HLA genotypes* and methazolamide-induced cADRs

303 **Fig. 2.** Forest plots of the associations between *HLA genotypes* and methazolamide-induced SJS/TEN

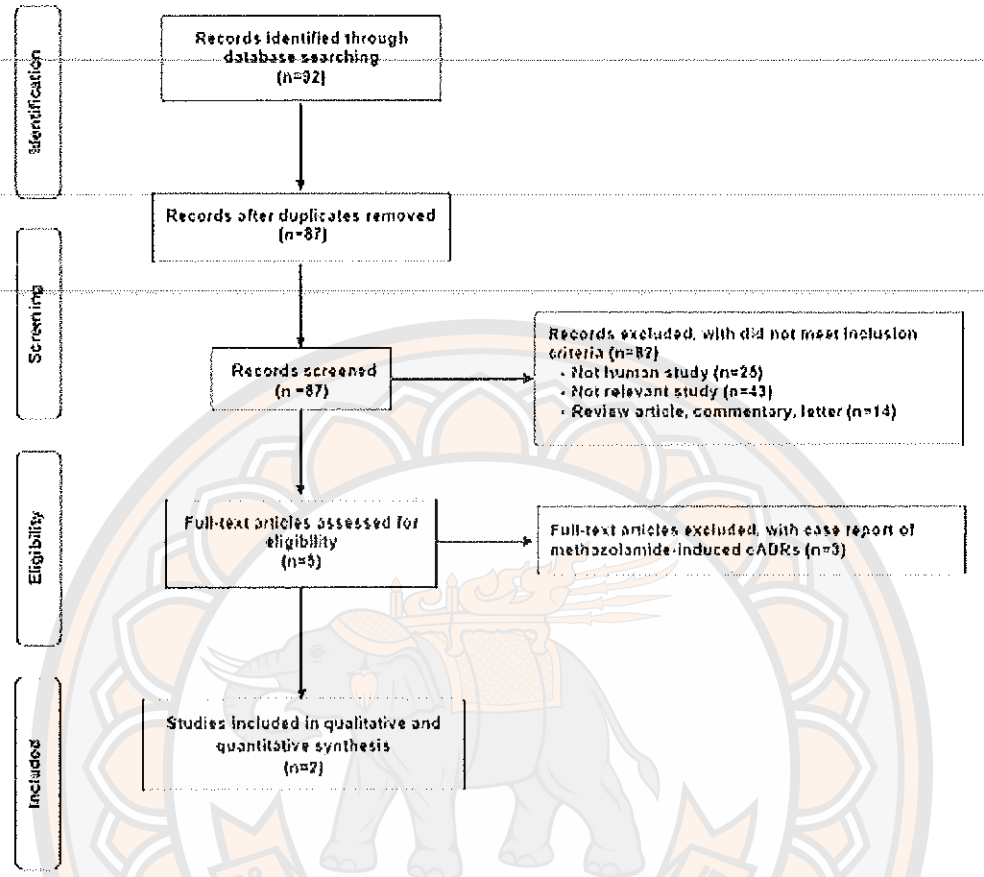

Fig. 1. PRISMA flow diagram of *HLA genotypes* and methazolamide-induced cADRs

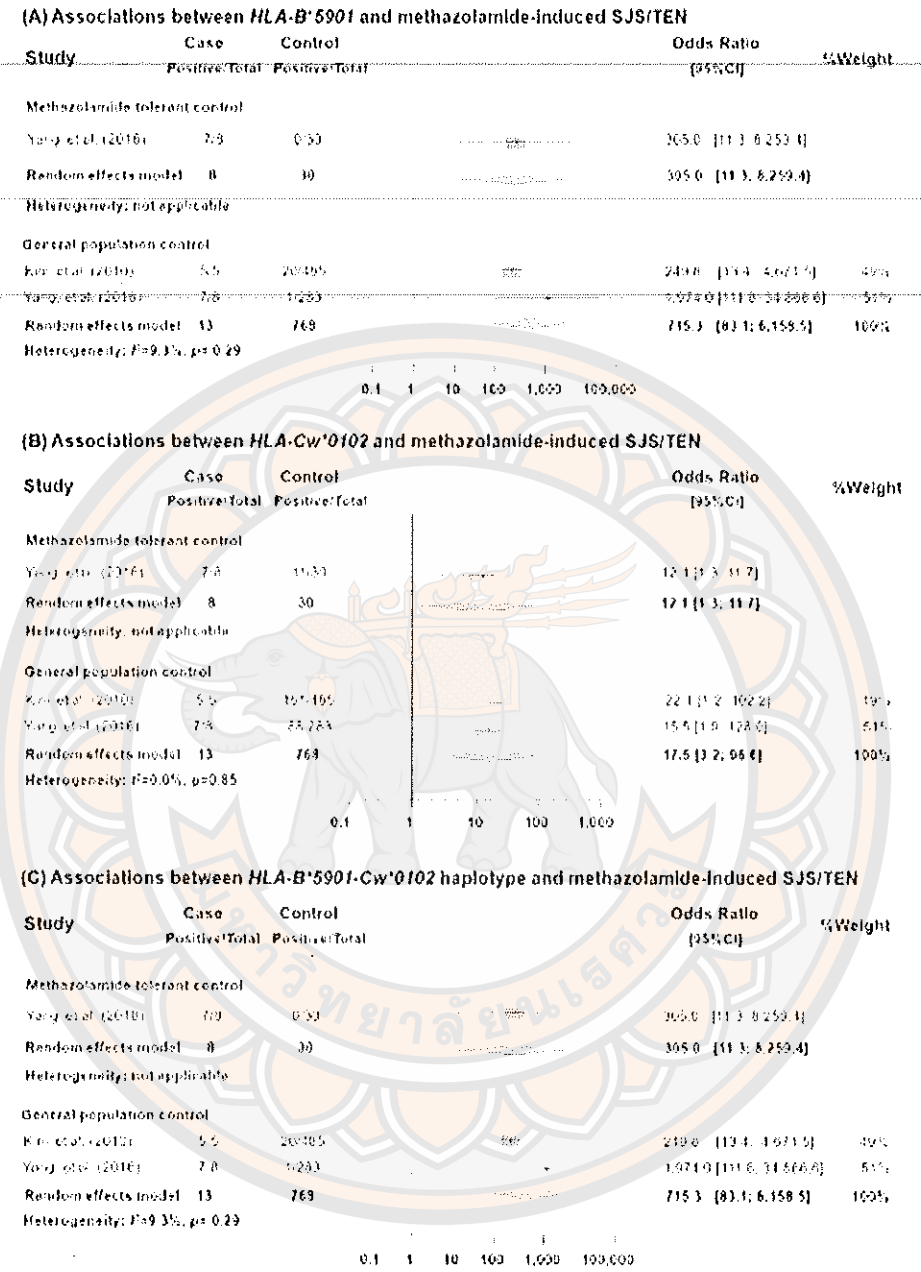

Fig. 2. Forest plots of the associations between *HLA genotypes* and methazolamide-induced SJS/TEN

Table 1. Characteristics of included studies

Author (Year)	Ethnicity	*HLA genotypes*	Type of cADRs (n)	Control (n)	Diagnostic criteria		NOS[a]
					Case	Control	
Kim, et al. (2010) [30]	Korean	*HLA-A*2402, HLA-B*5901, HLA-Cw*0302*	SJS/TEN (n=5)	General population (n=485)	SJS and TEN were defined as mucocutaneous disorders characterized by extensive erythema, blistering, epidermal detachment, erosions, exanthema and high fever. The diagnostic criteria of SJS/TEN were based on the clinical morphology described by Roujeau[5] (SJS: skin detachment of <10% of total body surface area; SJS/TEN overlap: skin detachment of 10–30%; TEN: skin detachment of >30%). All subjects were thoroughly reviewed by allergy specialists and dermatologists for accurate phenotype diagnosis and confirmation of methazolamide as a causative agent.	*HLA genotypes* information obtained from Lee et al.[44]	6
Yang, et al. (2016) [32]	Han Chinese	*HLA-B*5901, HLA-Cw*0102*	SJS/TEN (n=8)	General population (n=283)	Subjects who developed SJS or TEN symptoms within the first 2 months after methazolamide treatment and the symptoms resolved after withdrawal of the drug. SJS, overlap SJS/TEN and TEN were defined as epidermal detachment of skin detachment less than 10%, 10–30%, and >30% of total body surface area, respectively. Diagnoses of SJS and TEN were confirmed by two independent dermatologists who examined photographs, pathological slides and medical records.	*HLA genotypes* information of healthy southern Han Chinese subjects obtained from the human major histocompatibility complex database	7
				Methazolamide-tolerant control (n=30)		Subjects who did not develop any cutaneous manifestations at least 3 months after methazolamide treatment	

Abbreviations: cADRs = cutaneous adverse reactions; HLA = human leukocyte antigen; NOS = The Newcastle-Ottawa scale; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis

Footnote: [a] The Newcastle-Ottawa scale (NOS) is a tool commonly used for evaluating the quality of the selected studies based on 3 following domains. Those are 1) Selection (4 points), 2) Comparability (2 points) and 3) Exposure (4 points).[35] The total points of an evaluation are 10 points (range = 0-10 points). Thus, the more points awarded to the selected studies suggest a better quality of the studies.

Table 2. Calculated odds ratios of the included studies and summary odds ratios categorized by types of control and cADRs

Author (Year)	Type of cADRs	Ethnicity	*HLA genotypes* Positive/Total		Odds Ratio (95%CI)
			Case	Control	
HLA-B*5901					
Methazolamide tolerant control					
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	0/30	305.0 (11.3-8,259.4)
General population					
Kim, et al. (2010) [30]	SJS/TEN	Korean	5/5	20/485	249.8 (13.4-4,671.5)
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	1/283	1,974.0 (111.8-34,866.6)
Summary odds ratio (I^2=9.3%, p=0.29)					**715.3 (83.1-6,158.5)**
HLA-Cw*0102					
Methazolamide tolerant control					
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	11/30	12.1 (1.3-111.7)
General population					
Kim, et al. (2010) [30]	SJS/TEN	Korean	5/5	20/485	22.1 (1.2-402.2)
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	88/283	15.5 (1.9-128.0)
Summary odds ratio (I^2=0%, p=0.85)					**17.5 (3.2-96.6)**
HLA-B*5901, HLA-Cw*0102					
Methazolamide tolerant control					
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	0/30	305.0 (11.3-8,259.4)
General population					
Kim, et al. (2010) [30]	SJS/TEN	Korean	5/5	20/485	249.8 (13.4-4,671.5)
Yang, et al. (2016) [32]	SJS/TEN	Han Chinese	7/8	1/283	1,974.0 (111.8-34,866.6)
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Abbreviations: 95%CI = 95%confidence intervals; cADRs = cutaneous adverse reactions; HLA = human leukocyte antigen; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis