

# 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.

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## 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  $\leq 0.10$  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).

## 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 (range 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-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).

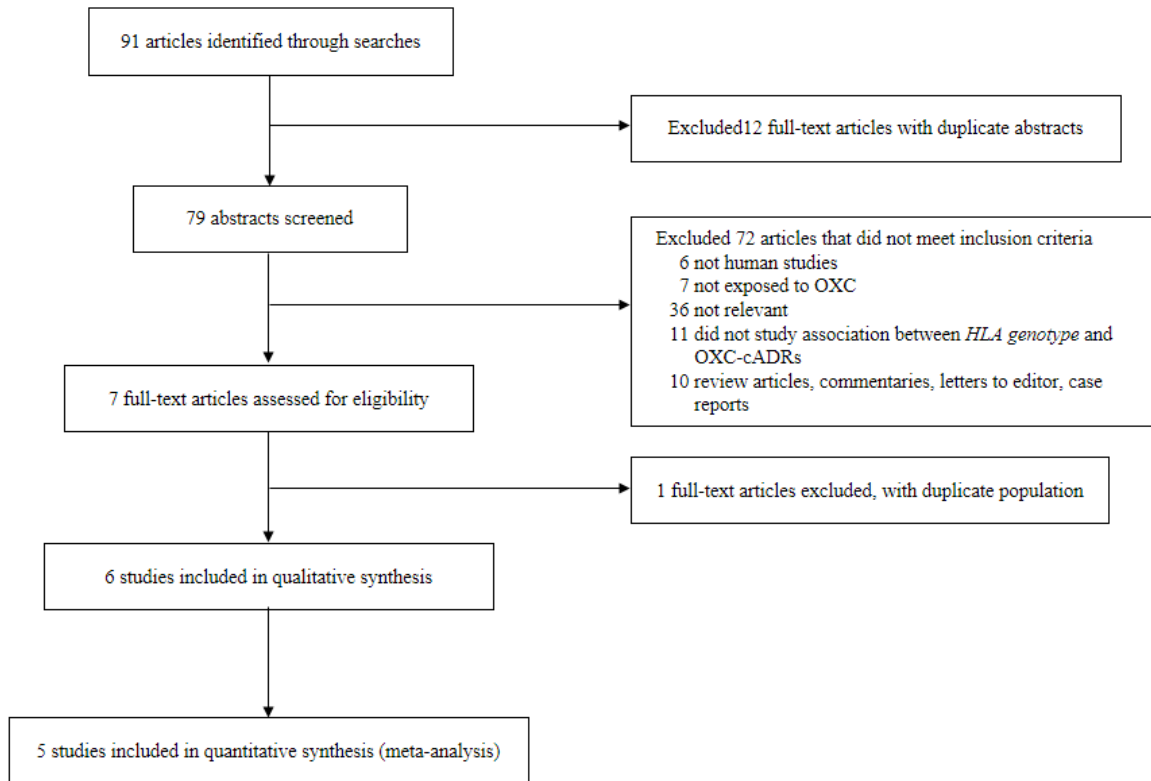


Figure 1 Summary of study identification, inclusion, and exclusion

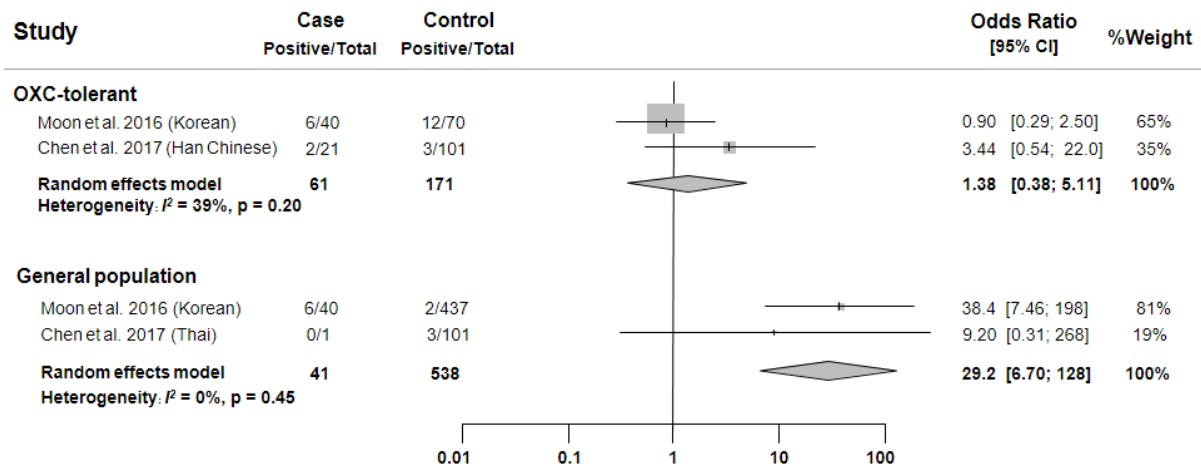
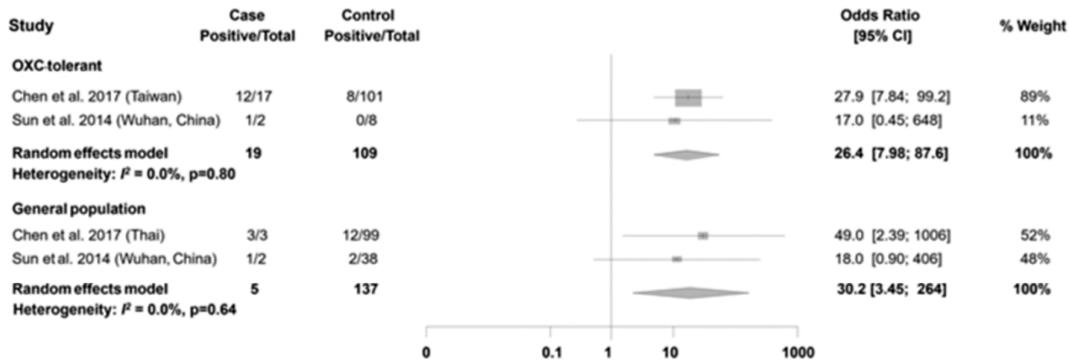
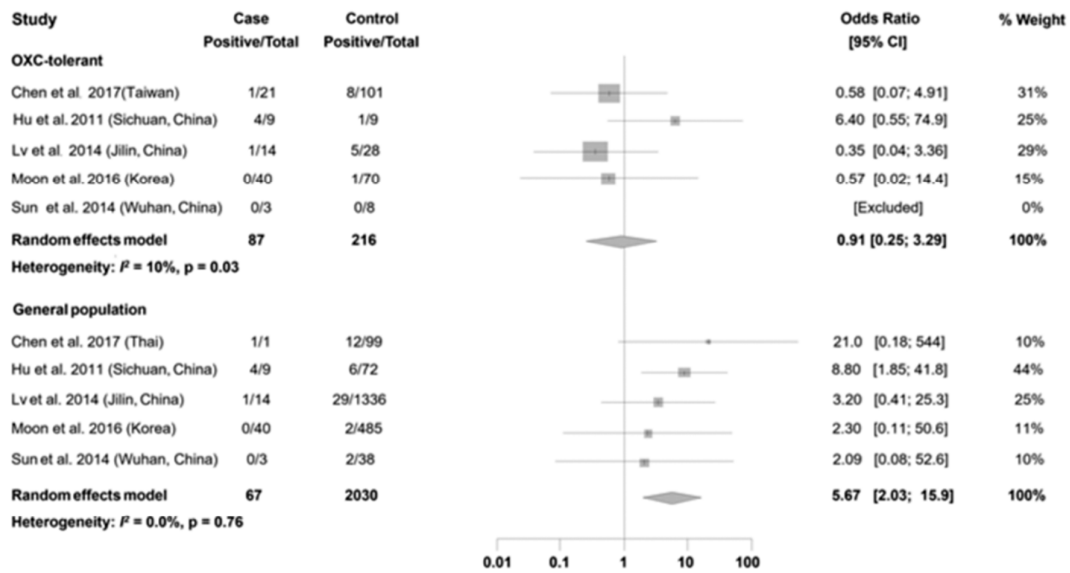


Figure 2 Forest plot of the associations between *HLA-A\*3101* and OXC-induced maculopapular rash

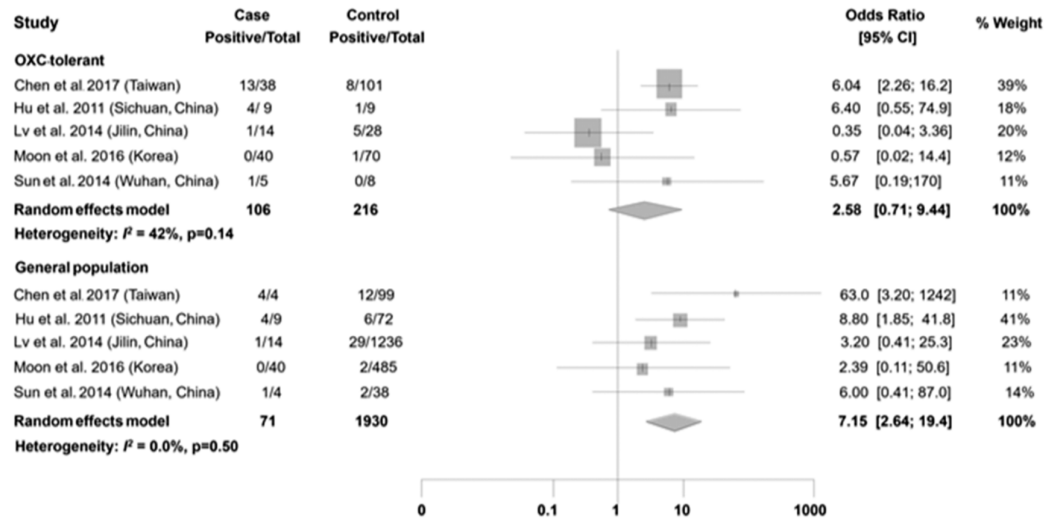
(A) *HLA-B\*1502* & Stevens-Johnson syndrome



(B) *HLA-B\*1502* & maculopapular rash



(C) *HLA-B\*1502* & Stevens-Johnson syndrome and maculopapular rash



**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).

### MHC class II and OXC-cADRs

The associations between MHC class II and OXC-cADRs are summarized in Table 3. Associations between *HLA-DQBI\*0501*, *HLA-DQBI\*0503*, *HLA-DRBI\*0403*, *HLA-DRBI\*0406*, and *HLA-DRBI\*1405* and with OXC-induced maculopapular rash in a Korean population were determined by Moon et al (21). *HLA-DRBI\*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 ethnicities 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.

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<b>Table 1.</b> Summary of studies investigating the association between <i>HLA</i> genotypes and OXC-cADRs										
Author (Year)	Country	Ethnicity	Study design	cADRs	Case (N)	Control (N)	MHC class I			MHC class II
							<i>HLA-A</i> genotypes	<i>HLA-B</i> genotypes	<i>HLA-C</i> genotypes	
Hu et al, 2011 (12)	Sichuan, China	Han Chinese	Case control	MP rash	9	OXC-tolerant: 9	ND	<i>HLA-B*1502</i>	ND	ND
						General population: 72				
He et al, 2012 (13)	Guangzhou, China	Han Chinese	Prospective cohort	MP rash	14	OXC-tolerant: 35	ND	<i>HLA-B*1302</i> <i>HLA-B*1501</i> <i>HLA-B*1502</i> <i>HLA-B*1519</i> <i>HLA-B*1527</i> <i>HLA-B*2704</i> <i>HLA-B*2709</i> <i>HLA-B*3905</i> <i>HLA-B*4001</i> <i>HLA-B*4601</i> <i>HLA-B*4804</i> <i>HLA-B*4901</i> <i>HLA-B*5101</i> <i>HLA-B*5401</i> <i>HLA-B*5604</i>	ND	ND
						General population: 264 (southern Han Chinese population), 569 (Hong Kong Chinese population), 106 (Guangzhou Han Chinese population)				
Lv et al, 2014 (22)	Jilin, China	Han Chinese	Case control	MP rash	14	OXC-tolerant: 28	ND	<i>HLA-B*0705</i> <i>HLA-B*1301</i> <i>HLA-B*1302</i> <i>HLA-B*1301</i> <i>HLA-B*1501</i> <i>HLA-B*1502</i> <i>HLA-B*1511</i> <i>HLA-B*1513</i> <i>HLA-B*1527</i> <i>HLA-B*1542</i> <i>HLA-B*1558</i> <i>HLA-B*2705</i> <i>HLA-B*3508</i> <i>HLA-B*3531</i> <i>HLA-B*3710</i> <i>HLA-B*3801</i> <i>HLA-B*3802</i> <i>HLA-B*3901</i>	ND	ND
						General population: 618 (Beijing Shijiazhuang Tianjin Han population), 105 (North Han Chinese population)				

<b>Table 1 Continued...</b>										
								<i>HLA-B*4001</i> <i>HLA-B*4006</i> <i>HLA-B*4402</i> <i>HLA-B*4403</i> <i>HLA-B*4601</i> <i>HLA-B*4701</i> <i>HLA-B*4801</i> <i>HLA-B*4804</i> <i>HLA-B*5101</i> <i>HLA-B*5102</i> <i>HLA-B*5201</i> <i>HLA-B*5301</i> <i>HLA-B*5501</i> <i>HLA-B*5502</i> <i>HLA-B*5601</i> <i>HLA-B*5604</i> <i>HLA-B*5801</i>		
Sun et al, 2014 (14)	Wuhan, China	Han Chinese	Case control	MP rash	1	OXC-tolerant: 8	ND	<i>HLA-B*1502</i>	ND	ND
						General population: 38				
				SJS	2	OXC-tolerant: 8				
						General population: 38				
Moon et al, 2016 (21)	Korea	Korean	Case control	MP rash	40	OXC-tolerant: 70	<i>HLA-A*3101</i> <i>HLA-A*3201</i>	<i>HLA-B*1501</i> <i>HLA-B*1502</i> <i>HLA-B*1511</i> <i>HLA-B*4002</i>	ND	<i>HLA-DQBI*0501</i> <i>HLA-DQBI*0503</i> <i>HLA-DRBI*0403</i> <i>HLA-DRBI*0406</i> <i>HLA-DRBI*1405</i>
Chen et al, 2017 (23)	Taiwan	Han Chinese	Case control	MP rash	21	General population: 101	<i>HLA-A*3101</i>	<i>HLA-B*1502</i>	ND	ND
				SJS	17					
				DRESS	6					
				BFDE	101					
	Thailand	Thai		MP rash	1	OXC-tolerant: 99				
				SJS	3					

**Table 1. Continued...**

Abbreviations: 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; ND = Not determined; OXC = oxcarbazepine; SJS = Stevens–Johnson syndrome.

<b>Table 2</b> Summary of cutaneous adverse drug reactions (cADRs) definition and diagnostic criteria of the selected studies									
Author (Year)	Country	Ethnicity	Type of cADRs	Definition of cADRs	Diagnostic criteria		cADRs evaluation	Assessing attribution of cADRs to OXC	NOS
					Case	Control			
Hu et al, 2011 (12)	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	NA	Epilepsy center	6
He et al, 2012 (13)	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	Epileptologist and dermatologist	9
Lv et al, 2014 (22)	Jilin, China	Han Chinese	MP rash	MP rash was defined as erythematous exanthema without blistering or postulation.	NA	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	NA	Epileptologist and dermatologist	6
Sun et al, 2014 (14)	Wuhan, China	Han Chinese	MP rash SJS	NA SJS was defined as skin detachment of 10% of total body-surface area.	Subjects who had cADRs within the first 8 weeks of exposure with improvement after drug withdrawal	General population: Healthy Han Chinese children OXC-tolerant: Subjects who had been on OXC for more than 2 months and no cADRs	NA	Dermatologists	6
Moon et al, 2016 (21)	Korea	Korean	MP rash	NA	Patients who experienced OXC-induced MP rash	General population: Using the HLA-B allele frequency reported Lee et al, 2005	NA	NA	5

Table 2.	Continued..					OXC-tolerant: Patients who tolerant of OXC			
Chen et al, 2017 (23)	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 $\geq 4$ or Naranjo algorithm $\geq 5$ ) were recruited.	General population: NR	At least 2 dermatologists	NA	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.					
			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.					
			BFDE	BFDE was characterized by recurrent with dusky					
OXC-tolerant: Patients who are tolerant of OXC									

<b>Table 2.</b>	<b>Continued..</b>			red or heavy pigmented eruptions with blisters mostly on the same sites with re-exposure to the causative agents.					
Abbreviations: 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									

<b>Table 3.</b> Summary odds ratios of the included studies categorized by <i>HLA genotypes</i> and OXC-cADRs											
<i>HLA genotypes</i>	cADRs	Author	Year	Race (Country)	Study design	Case		Control		OR (95%CI)	
						HLA positive	HLA negative	HLA positive	HLA negative		
<b>MHC class I</b>											
<b><i>HLA-A genotypes</i></b>											
<i>HLA-A*3101</i>	MP rash	General population control									
		Moon et al (21)	2016	Korean (Korea)	Case control	6	34	2	483	38.4 (7.46-198)	
		Chen et al (23)	2017	Thai (Thailand)	Case control	0	1	3	96	9.20 (0.31-268)	
		Subtotal ( $I^2= 0.0\%$ , $P = 0.45$ )									29.2 (6.70-128) <sup>a</sup>
		OXC-tolerant									
		Moon et al (21)	2016	Korean (Korea)	Case control	6	34	12	58	0.90 (0.29-2.50)	
		Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	2	19	3	98	3.44 (0.54-22.0)	
		Subtotal ( $I^2= 39\%$ , $P = 0.20$ )									1.38 (0.38-5.11)
	SJS	General population control									
		Chen et al (23)	2017	Thai (Thailand)	Case control	0	3	3	96	3.94 (0.17-91.9)	
		OXC-tolerant									
		Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	1	16	3	98	2.04 (0.20-20.9)	
	DRESS	OXC-tolerant									
		Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	0	6	3	98	2.16 (0.10-46.5)	
BFDE	OXC-tolerant										
	Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	0	2	3	98	5.63 (0.23-141)		

<b>Table 3. Continued...</b>										
<i>HLA-A*3201</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	2	38	3	482	8.46 (1.37-52.2) <sup>a</sup>
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	2	38	1	69	3.63 (0.32-41.4)
<b><i>HLA-B genotypes</i></b>										
<i>HLA-B*0705</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*1301</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	1	27	2.08 (0.12-35.9)
<i>HLA-B*1302</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	3	11	3	32	2.91 (0.51-16.6)
		Lv et al (22)	2014	Han Chinese (China)	Case control	2	12	4	24	1.00 (0.16-6.25)
<i>HLA-B*1315</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*1501</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	2	26	1.00 (0.08-12.1)
		Moon et al (21)	2016	Korean (Korea)	Case control	2	38	16	54	0.18 (0.04-0.82)
		Subtotal ( $I^2= 27\%$ , $P = 0.24$ )								
		OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	3	32	0.82 (0.08-8.63)
<i>HLA-B*1502</i>	MP rash	General population control								
		Hu et al (12)	2011	Han Chinese (China)	Case control	4	5	6	66	8.80 (1.85-41.8)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	29	1207	2.09 (0.08-52.6)
		Sun et al (14)	2014	Han Chinese (China)	Case control	0	3	2	36	3.20 (0.41-25.3)
		Moon et al (21)	2016	Korean (Korea)	Case control	0	40	2	483	2.30 (0.11-50.6)
		Chen et al (23)	2017	Thai (Thailand)	Case control	1	0	12	87	21.0 (0.18-544)
		Subtotal ( $I^2= 0.0\%$ , $P = 0.76$ )								
		OXC-tolerant								
		Hu et al (12)	2011	Han Chinese (China)	Case control	4	5	1	8	6.40 (0.55-74.9)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	5	23	0.35 (0.04-3.36)
		Sun et al (14)	2014	Han Chinese (China)	Case control	0	3	0	8	(Excluded)
		Moon et al (21)	2016	Korean (Korea)	Case control	0	40	1	69	0.57 (0.02-14.4)
		Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	1	20	8	93	0.58 (0.07-4.91)
Subtotal ( $I^2= 10\%$ , $P = 0.03$ )										

Table 3. Continued...		OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	2	33	1.27 (0.11-15.2)
SJS	General population control									
	Sun et al (14)	2014	Han Chinese (China)	Case control	1	1	2	36	18.0 (0.90-406)	
	Chen et al (23)	2017	Thai (Thailand)	Case control	3	0	12	87	49.0 (2.39-1006)	
	Subtotal ( $I^2= 0.0\%$ , $P = 0.80$ )								30.2 (3.45-264) <sup>a</sup>	
	OXC-tolerant									
	Sun et al (14)	2014	Han Chinese (China)	Case control	1	1	0	8	17.0 (0.45-648)	
	Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	12	5	8	93	27.9 (7.84-99.2)	
	Subtotal ( $I^2= 0.0\%$ , $P = 0.64$ )								26.4 (7.98-87.6) <sup>a</sup>	
	MP rash+SJS	General population control								
		Hu et al (12)	2011	Han Chinese (China)	Case control	4	5	6	66	8.80 (1.85-41.8)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	29	1207	3.20 (0.41-25.3)
		Sun et al (14)	2014	Han Chinese (China)	Case control	1	3	2	36	6.00 (0.41-87.0)
		Moon et al (21)	2016	Korean (Korea)	Case control	0	40	2	483	2.39 (0.11-50.6)
		Chen et al (23)	2017	Thai (Thailand)	Case control	4	0	12	87	63.0 (3.20-1242)
Subtotal ( $I^2= 0.0\%$ , $P = 0.50$ )								7.15 (2.64-19.4) <sup>a</sup>		
OXC-tolerant										
Hu et al (12)		2011	Han Chinese (China)	Case control	4	5	1	8	6.40 (0.55-74.9)	
Lv et al (22)		2014	Han Chinese (China)	Case control	1	13	5	23	0.35 (0.04-3.36)	
Sun et al (14)		2014	Han Chinese (China)	Case control	1	4	0	8	5.67 (0.19-170)	
Moon et al (21)		2016	Korean (Korea)	Case control	0	40	1	69	0.57 (0.02-14.4)	
Chen et al (23)		2017	Han Chinese (Taiwan)	Case control	13	25	8	93	6.04 (2.26-16.2)	
Subtotal ( $I^2= 42\%$ , $P = 0.14$ )								2.58 (0.71-9.44)		
DRESS	OXC-tolerant									
	Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	0	6	8	93	2.20 (0.10-49.7)	
BFDE	OXC-tolerant									
	Chen et al (23)	2017	Han Chinese (Taiwan)	Case control	0	2	8	93	0.85 (0.04-16.3)	
HLA-B*1511	General population control									
	Moon et al (21)	2016	Korean (Korea)	Case control	1	39	19	466	0.63 (0.11-6.97)	
	OXC-tolerant									
	Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	2	26	0.37 (0.02-8.14)	
	Moon et al (21)	2016	Korean (Korea)	Case control	1	39	1	69	1.77 (0.11-29.1)	
Subtotal ( $I^2= 0.0\%$ , $P = 0.46$ )								0.87 (0.11-6.97)		
HLA-B*1513	OXC-tolerant									
	Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)	
HLA-B*1519	OXC-tolerant									
	He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)	
HLA-B*1527	OXC-tolerant									

<b>Table 3.</b> <b>Continued...</b>		He et al (13)	2012	Han Chinese (China)	Prospective cohort	2	12	0	35	14.0 (0.64-316)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*1542</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*1558</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*2704</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	2	12	0	35	14.2 (0.64-316)
<i>HLA-B*2705</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*2709</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
<i>HLA-B*3508</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*3531</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	2	26	0.37 (0.02-8.14)
<i>HLA-B*3710</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*3801</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*3802</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	3	11	2	25	3.41 (0.50-23.7)
<i>HLA-B*3901</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*3905</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
<i>HLA-B*4001</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	3	11	10	25	0.68 (0.16-2.97)
		Lv et al (22)	2014	Han Chinese (China)	Case control	2	12	4	24	1.00 (0.16-6.25)
<i>HLA-B*4002</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	10	30	37	448	4.04 (1.83-8.90) <sup>a</sup>
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	10	30	5	65	4.33 (1.36-13.8) <sup>a</sup>
<i>HLA-B*4006</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*4402</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)



<b>Table 3. Continued...</b>										
<i>HLA-B*4403</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	2	12	4	24	1.00 (0.16-6.25)
<i>HLA-B*4601</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	3	11	11	24	0.60 (0.14-2.6)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	3	25	0.64 (0.06-6.79)
<i>HLA-B*4701</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*4801</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	4	24	0.19 (0.01-3.74)
<i>HLA-B*4804</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	24	0.56 (0.02-14.8)
<i>HLA-B*4901</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
<i>HLA-B*5101</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	3	32	0.82 (0.08-8.63)
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	1	27	2.08 (0.12-35.9)
<i>HLA-B*5102</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*5201</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*5301</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*5401</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
<i>HLA-B*5501</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*5502</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	1	27	2.08 (0.12-35.9)
<i>HLA-B*5601</i>	MP rash	OXC-tolerant								
		Lv et al (22)	2014	Han Chinese (China)	Case control	1	13	0	28	6.33 (0.24-166)
<i>HLA-B*5604</i>	MP rash	OXC-tolerant								
		He et al (13)	2012	Han Chinese (China)	Prospective cohort	1	13	0	35	7.89 (0.30-206)
		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	1	27	0.63 (0.02-16.5)
<i>HLA-B*5801</i>	MP rash	OXC-tolerant								

<b>Table 3. Continued...</b>		Lv et al (22)	2014	Han Chinese (China)	Case control	0	14	3	25	0.25 (0.01-5.21)
<b>MHC class II</b>										
<i>HLA-DQB1*0501</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	1	39	3	482	4.12 (0.42-40.54)
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	1	39	7	63	0.23 (0.03-1.95)
<i>HLA-DQB1*0503</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	3	37	46	439	0.77 (0.23-2.61)
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	3	37	14	56	0.31 (0.09-1.21)
<i>HLA-DRBI*0403</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	7	33	31	454	3.11 (1.27-7.59) <sup>a</sup>
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	7	33	1	69	14.64 (1.73-124) <sup>a</sup>
<i>HLA-DRBI*0406</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	2	38	39	446	0.60 (0.14-2.59)
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	2	38	11	59	0.28 (0.06-1.34)
<i>HLA-DRBI*1405</i>	MP rash	General population control								
		Moon et al (21)	2016	Korean (Korea)	Case control	3	37	22	463	1.71 (0.49-5.97)
		OXC-tolerant								
		Moon et al (21)	2016	Korean (Korea)	Case control	3	37	11	59	0.43 (0.11-1.66)
Abbreviations: cADRs = cutaneous adverse drug 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										
Footnote: <sup>a</sup> Association with a statistical significance										