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Association between HLA-A*3201 allele and oxcarbazepine-induced cutaneous adverse reactions in Eastern Han Chinese population

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ABSTRACT

Purpose: To determine genetic associations between oxcarbazepine (OXC)-induced cutaneous adverse drug reactions (cADRs) and human leukocyte antigen (HLA) variants in the Eastern Han Chinese population.
Methods: A total of 120 patients were enrolled in this study, including 30 subjects with OXC-induced cADRs (case group) and 90 OXC-tolerant patients (control group). High-resolution HLA genotyping was conducted for HLA-A, HLA-B, HLA-C, and HLA-DRB1, and allele frequencies were compared.
Results: No patient carried the HLA-B *1502 allele in the case group, the frequency of HLA-B *1502 allele in the control group was 6.1%. HLA-A*3201 allele was detected in 13.3% of 30 patients with OXC-induced cADRs (4/30) and 0% of 90 OXC-tolerant patients (0/90). The difference in HLA-A*3201 frequency between the two groups was statistically significant [P = 0.004, odds ratio (OR) = 15.877, 95% confidence interval (CI) = 1.817-138.720].
Conclusions: Eastern Han Chinese patients with the HLA-A*3201 allele may be more susceptible to OXC-induced cADRs, while the HLA-B*1502 allele is not correlated with it. The precise association between HLA alleles and OXC-induced cADRs warrants further study.

1. Introduction

Epilepsy is one of the most common neurological conditions, with more than 2% of the population worldwide affected according to the latest study [1]. As a chronic disease, epilepsy requires long-term treatment with anti-epileptic drugs (AEDs) [2]. Moreover, up to 30% of patients with epilepsy remain resistant to the standard therapy despite the multitude of available AEDs such as carbamazepine (CBZ), sodium valproate, and phenytoin (PHT) [3,4]. Oxcarbazepine (OXC), a 10-keto derivative of CBZ, has emerged as a relatively new AED. Although the structures of OXC and CBZ are similar [5], OXC is associated with improved tolerability and safety profiles in epileptic patients with reduced potential for drug interactions [6,7]. It has been prescribed as monotherapy or adjunctive therapy; however, several side effects of OXC have also been reported, including somnolence, fatigue, dizziness, headache, and nausea as the most common side effects similar to other AEDs, along with skin eruption and leukopenia. In particular, cutaneous adverse drug reactions (cADRs) to AEDs are considered to be a prevalent issue in the course of medical treatment for epilepsy [8,9], with an incidence of 5-9% [10–12], which result in drug termination and initiation of new therapeutic options in nearly all cases [11]. OXC-induced cADRs show various clinical presentations ranging from mild maculopapular eruption (MPE) to the more severe cutaneous reactions, which seriously endanger the life of the patient, comprising Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) [13–17]. Although OXC is applied just as frequently as CBZ in the therapy of partial epilepsy [18–20], few studies have focused on its effects on cADRs.

Human leukocyte antigen (HLA) genetic variants have been associated with cADRs to CBZ; however, little is known about this association with respect to OXC. Recently, HLA-B*1502 allele, which is considered to be closely related to CBZ-induced SJS/TEN, has been a target of several pharmacogenetic studies in Asian populations [14,21–25]. Moreover, genetic information on potential associations is required to be included on the CBZ label as updated by the United States Food and Drug Administration. Thus, before initiating CBZ therapy, genetic screening for the HLA-B*1502 allele is recommended

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for Asian patients [26]. Accordingly, researchers have begun to pay more attention to the potential impact of HLA alleles in OXC-induced cADRs, and recent studies have provided evidence of a potential association with the HLA-A*3101, HLA-B*3802, HLA-B*1302, HLA-B*4002 and HLA-DRB1*04:03 alleles [27–30].

The objective of the present study was to determine the correlation between OXC-induced cADRs and HLA alleles in 120 subjects of the Eastern Han Chinese population, including the HLA-A, HLA-B, HLA-C, and HLA-DRB1 alleles. This study represents the largest genetic association study on OXC-induced cADRs conducted to date. These results can provide insight into the mechanisms contributing to cADRs and serve as guidance for proper therapeutic decisions at the individual level.

2. Methods

2.1. Study design

We conducted a case-control genetic association study from January 2011 to December 2016 at Huai'an Third People's Hospital, Jiangsu Province and Ruijin Hospital, Shanghai Jiaotong University School of Medicine. This research was approved by the Ethics Committee of Huai'an Third People's Hospital and Ruijin Hospital in conformation with the Helsinki Declaration, Good Clinical Practice, and local regulations. Informed consent was obtained from all patients before any trial-related procedures were performed.

2.2. Subjects

This case-control association study involved 120 subjects (2-49 years old), including 30 patients with OXC-induced cADRs (case group) and 90 OXC-tolerant patients (control group). All subjects were of indigenous Eastern Han Chinese ethnicity and were successively recruited from Huai'an Third People's Hospital and Ruijin Hospital. On the basis of the recent proposal by the International League Against Epilepsy (ILAE), epilepsy was defined according to the following conditions: (a) at least two unprovoked seizures (or reflex seizures) occurring at least 24 h apart; (b) after two unprovoked seizures, the risk of a recurrent unprovoked seizure (or reflex seizure) was at least 60% in the following 10 years; and (c) an epilepsy syndrome diagnosis [31]. The eligibility criteria included patients with a history of partial seizures, simple, complex, or evolving into secondarily generalized seizures, and/or primary GTC seizures that had experienced at least one seizure during the last 2 months. The 90 OXC-tolerant patients, enrolled as tolerant controls, had been taking OXC for at least 3 months with generally good tolerance and no cADR. The exclusion criteria were as follows: (1) history of status epilepticus three months before randomization of the study, (2) history of benzodiazepines intake more than once, (3) history of barbiturates intake at a dose of 15 mg/kg or higher, (4) history of significant clinical diseases or psychiatric disorders, (5) history of progressive structural neurologic diseases, (6) diagnosis of non-epileptic seizures, (7) suspected alcohol or drug addiction 12 months preceding randomization of this study, (8) participation in any other clinical trial of drugs within 60 days preceding randomization or in the course of the study, (9) medication history of dihydropyridine calcium channel blockers or monoamine oxidase inhibitors, (10) hyper-sensitivity to OXC or its metabolites, (11) previous treatment with OXC, and (12) history of non-compliance.

2.3. Drug administration schedule and cADR assessment

For all patients, OXC was administered orally according to the following therapeutic schedule. Patients with newly diagnosed epilepsy were given OXC monotherapy, whereas those taking some other AEDs for treatment were given OXC added to their original medication. For adult patients (> 14 years old), the starting dose of OXC was 300-600 mg/day and the medicinal dosage was increased by 150 mg via titration, until 600-1200 mg/day. For children (≤14 years old), the initial dose of OXC was set as $8\ mg\ kg^{-1}\cdot day^{-1}$, and the medicinal dosage was increased by $8\ mg\ kg^{-1}$ weekly until reaching the maintenance dosage of $20–30\ mg\ kg^{-1}\cdot day^{-1}$. The exact maintenance dosage depends on the curative effect and drug reactions. If the medicinal dosage for a child according to the pediatric therapeutic schedule based on body weight was calculated to be higher than that determined for an adult, the child was administered the adult therapeutic schedule. In consideration of the latency of cADRs, in which the initial symptoms most commonly appear within the first 8 weeks after OXC administration, all subjects were observed for at least 3 months [32,33].

After administration of OXC, epileptologists collaborated with dermatologists to evaluate and diagnose cADRs, and to determine the attribution of cADRs to OXC. Patients with OXC-induced cADRs, including MPE, SJS, TEN, and DRESS, were referred to a dermatologist for further evaluation. The characteristics of MPE include cutaneous itch, erythema, and papules without blistering or pustulation. After withdrawal, the symptoms of MPE generally resolve spontaneously within 1-2 weeks [34]. The diagnosis of SJS and TEN was made in reference to Roujeau's diagnostic criteria [35], including clinical manifestations of exfoliation and necrosis of the epidermis, mucosal involvement, speedy development, followed by fever and other systemic damage. The clinical manifestations of DRESS are fever, rash, and eosinophilia accompanied by systemic symptoms such as hepatitis and nephritis.

The patient demographics, type of seizure, medical history, concomitant AEDs, cross-sensitivity with other AEDs, initiation and expiry date of OXC treatment, initial dose and maintenance dosage of OXC treatment, dates and clinical manifestations of OXC-induced cADRs, therapeutic methods for OXC-induced cADRs, and adjustments to AEDs were documented throughout the study.

2.4. HLA-A, HLA-B, HLA-C, and HLA -DRB1 genotyping

A peripheral blood sample of approximately 8.0 ml was collected from all subjects. Genomic DNA was extracted from peripheral blood lymphocytes according to the standard phenol-chloroform method. Polymerase chain reaction with sequence-specific primers was performed to identify the presence of HLA. MiSeq Benchtop Sequencer (Illumina, USA) was then applied to sequence the samples from patients in the case and control groups to obtain the four-digit HLA allele genotypes of all subjects. The results of HLA genotyping were well documented in the form of the exact genotype of the four target HLA alleles.

2.5. Statistical analysis

SPSS software version 24.0 was used for all statistical analyses. To reduce bias in estimating the odds ratio, whenever a zero-count cell was encountered, 0.5 was added to all cells in the 2×2 table. Descriptive statistics are shown as mean ± standard deviation. Two-by-two chi-square tests and Fisher's exact tests were performed to compare the allele carrier rates between OXC-cADRs cases and OXC-tolerant controls. Two sided P-values of < 0.05 were considered to be statistically significant.

3. Results

3.1. Characteristics of the study population

There were no significant differences in the baseline characteristics between the patients showing OXC-induced cADRs and those with OXC tolerance (Table 1). Among the 30 patients with OXC-induced cADRs, four were diagnosed with generalized seizure, whereas the others were diagnosed with partial seizure or secondary seizure. Two patients were diagnosed as benign epilepsy of childhood with centro-temporal EEG foci and two were temporal lobe epilepsy. The demographic and clinical

Table 1
Comparison of patient baseline characteristics between the two groups.

Characteristics of patients with OXC-induced cADRs and OXC-tolerant			
	OXC-induced cADRs (No.patients = 30)	OXC-tolerant (No.patients = 90)	P-value
Age Mean(SD) [Median(range)]	18.57(12.80) [14(2-44)]	21.37(11.69) [19(5-49)]	t-test,p = 0.270
Sex Male(% total) Female(% total)	16(53.33) 14(46.67)	39(43.33) 51(56.67)	c2,d.f.(l),p = 0.400
Allergy history(% total)	1(3.33)	3(3.33)	c2,d.f.(l),p = 1.000
Generalized seizure(% total)	4(13.33)	6(6.67)	c2,d.f.(l),p = 0.266
Epileptic syndrome(% total)	4(13.33)	3(3.33)	c2,d.f.(l),p = 0.065
Initial dose ≤450 mg/day (% total) >450 mg/day (% total)	20(66.67) 10(33.33)	48(53.33) 42(46.67)	c2,d.f.(l),p = 0.287

features of the patients with OXC-induced cADRs are summarized in Table 2. The median age of patients with OXC-induced cADRs was 18.57 ± 12.80 years (range 2-44 years); 15 (50.00%) of the patients were adults aged older than 14 years and 16 (53.33%) were male (Table 1).

3.2. cADRs

Among 30 patients in the case group, 24 patients merely experienced an OXC-related rash. The other six patients (20%) presented generalized manifestations such as fever in addition to the rash, of which two patients (case 4 and 19) showed elevated alanine aminotransferase levels. One patient (case 4) was considered to exhibit AED hypersensitive syndrome (Table 2). However, none of the cases progressed to severe cADRs such as SJS, TEN, and DRESS. The median interval from initial administration to the allergic dose of OXC was 6.43 ± 5.48 days (range 1-20 days), and the median latency of OXC-induced cADRs was 11.33 ± 5.18 days (range 2-23 days).

An antihistamine or short-term steroid was administered after the immediate discontinuation of OXC upon symptom development. After the withdrawal of OXC, the patients' conditions improved and recovered within 4 weeks without hospitalization. Only one patient (3.33%) had a history of another AED allergy, and no patient had a history of allergic reactions to other medicines (Tables 1 and 2).

3.3. HLA-A, HLA-B, HLA-C, and HLA-DRB1 genotyping

We compared the frequencies of HLA-A, HLA-B, HLA-C, and HLA-DRB1 alleles between the 30 patients with OXC-induced cADRs and the 90 OXC-tolerant patients. The HLA-B *1502 allele, which was previously reported to be strongly associated with CBZ-induced hypersensitivity [26], was not detected among the patients with OXC-induced cADRs in our study, while the frequency of HLA-B *1502 allele in the control group was 6.1%. HLA-A*3201 allele was detected in 13.3% of 30 patients with OXC-induced cADRs (4/30) and 0% of 90 OXC-tolerant patients (0/90). The difference in HLA-A*3201 frequency between the two groups was statistically significant [P = 0.004, odds ratio (OR) = 15.877, 95% confidence interval (CI) = 1.817-138.720]. Detailed information on the HLA allele frequencies is shown in Tables 2 and 3 and Supplementary Table 1.

4. Discussion

cADRs to AEDs are considered to be more common and more severe in older AEDs such as CBZ [36]. OXC, as a new anti-convulsant medicine, has been used as a treatment for partial seizures in adults and children since 2000 [37]. Owing to differences in their metabolic pathways, OXC is generally considered to be much safer than CBZ. The mechanisms of OXC and its pharmacologically active 10-monohydroxy derivative are mainly based on blocking voltage-sensitive sodium channels, leading to stabilization of overexcited neural membranes, inhibition of repetitive neuronal electro discharge, and consequent reduction of the spread of synaptic impulses [38–40]. Furthermore, OXC can increase potassium ion conduction and regulate high pressure-activated calcium channels, which may also contribute to its spasmolytic action. Moreover, OXC has also been prescribed to treat diseases other than epilepsy, including for pain control [41,42] and emotional disorders [43,44]. In recent clinical researches concerned with the administration of OXC to those diseases have found some adverse effects inclusive of rash likewise, which made patients withdrew prematurely in general [45]. Therefore, it is particularly important to understand and predict the common factors of OXC allergy.

Genetic susceptibility has been deemed as an important predictor for AEDs-induced cADRs. For the past few years, HLA-B*1502 has been reported to be closely associated with the risk of developing SJS/TEN after CBZ administration among East Asians [46], but not related to CBZ-induced MPE [23]. HLA-B*1502 was detected in 70.59% cases(12/17)of OXC-induced SJS in Taiwan and in all cases (3/3) of OXC-induced SJS in Thailand [47]. This suggests an unusually strong correlation between the HLA-B*1502 allele and OXC-induced SJS/TEN in these populations. A latest meta-analysis including 229 patients with OXC-cADRs, 251 OXC-tolerant patients, and 2358 participants from general populations of Han Chinese, Korean, and Thai ethnicities has found the same associations between HLA-B*1502 and OXC-induced SJS [29]. A study involving 40 patients with OXC-induced MPE and 70 OXC-tolerant patients found that HLA-B*40:02 and HLA-DRB1*04:03 alleles were significantly associated with OXC-induced MPE in Korean population, other than HLA-B*15:02, HLA-A*31:01 and HLA-B*15:11, which were well-known HLA-related risk factors for CBZ-induced cADRs [30]. Although different results revealed that HLA-B*1502 and HLA-A*3101 alleles were significantly associated with OXC-induced maculopapular rash [29]. Two recent meta-analyses have revealed that HLA-A*2402 is associated with the susceptibility to aromatic antiepileptic drugs-induced MPE in Chinese population, while neither of them has taken OXC into account [46,48]. The exact associations between OXC-induced cADRs and HLA alleles remain to be demonstrated. To our knowledge, our present study includes the largest number of OXC-induced MPE patients and OXC-tolerant patients among studies in Chinese population aimed at revealing the genotype-phenotype relationship conducted to date. Through this analysis, we determined that HLA-B*1502 is in fact not related to OXC-induced MPE in the Eastern Han Chinese population, similar to the previous results for CBZ [23]. Our result is in line with previous work conducted in southern and northern Han Chinese populations [27,28], but is distinct from another study revealing a significant correlation between OXC-induced MPE and HLA-B*1502 allele in central Han Chinese patients [49]. These differences likely reflect diversity in the genetic background, and highlight the importance of consideration of regional and ethnic differences for assessing genotype-phenotype associations. In addition, some previous studies focused specifically on OXC-induced SJS/TEN while others evaluated only MPE. Moreover, the frequency of the HLA-B*1502 allele itself may vary among populations, contributing to the conflicting results. It is worth noting that the sample size was very small in these previous studies, which limited the ability to conduct appropriate statistical analysis. The results of our case-control study suggest that individuals of the Chinese Eastern Han population with HLA-A*3201

Table 2
Demographic and clinical characteristics of patients with OXC-induced cADRs(n = 30).

Patient	Sex	Age (years)	Duration	Seizure Type	History of Other AED Allergy	Latency to cADRs (days)	cADRs type		HLA-A*3201
							Skin Manifestations	Systemic Symptoms	
1	F	8	1M	Partial seizure	None	10	Generalized rash	Fever	Negative
2	M	10	3d	Partial seizure	None	19	Maculopapular erythema	None	Negative
3	F	23	2Y	Partial seizure	None	8	Maculopapular erythema	None	Negative
4	M	40	7Y	Partial seizure	None	9	Generalized rash	Fever, ALT↑, AHS	Negative
5	M	42	2Y	Generalized seizure	None	2	Maculopapular erythema	None	Negative
6	F	44	6Y	Partial seizure	None	7	Maculopapular erythema	None	Negative
7	M	11	4Y	Partial seizure	None	11	Maculopapular erythema	None	Negative
8	M	11	5Y	Partial seizure	Lamotrigine	7	Maculopapular erythema	None	Negative
9	F	17	2Y	Partial seizure	None	10	Maculopapular erythema	None	Negative
10	M	23	2Y	Partial seizure	None	22	Maculopapular erythema	None	Positive
11	F	40	5M	Partial seizure	None	20	Maculopapular erythema	None	Negative
12	M	44	1Y	Partial seizure	None	10	Maculopapular erythema	None	Negative
13	M	9	10d	Partial seizure	None	14	Generalized rash	Fever	Negative
14	M	19	2Y	Partial seizure	None	8	Maculopapular erythema	None	Negative
15	F	19	7M	Partial seizure	None	12	Maculopapular erythema	None	Negative
16	M	28	6M	Partial seizure	None	21	Maculopapular erythema	None	Negative
17	F	5	1M	Partial seizure	None	10	Generalized rash	Fever	Negative
18	M	28	7Y	Partial seizure	None	23	Maculopapular erythema	None	Negative
19	M	8	2M	Partial seizure	None	14	Generalized rash	Fever, ALT↑	Negative
20	F	10	5Y	Partial seizure	None	9	Maculopapular erythema	None	Negative
21	M	6	1Y	Generalized seizure	None	3	Generalized rash	Fever	Negative
22	F	2	4d	Generalized seizure	None	12	Maculopapular erythema	None	Negative
23	F	12	4Y	Generalized seizure	None	10	Maculopapular erythema	None	Positive
24	F	8	5Y	Partial seizure	None	7	Maculopapular erythema	None	Negative
25	F	26	4Y	Partial seizure	None	7	Maculopapular erythema	None	Negative
26	M	22	19Y	Partial seizure	None	10	Maculopapular erythema	None	Negative
27	F	8	6M	Partial seizure	None	11	Maculopapular erythema	None	Negative
28	M	8	7M	Partial seizure	None	10	Maculopapular erythema	None	Positive
29	M	7	4Y	Partial seizure	None	10	Maculopapular erythema	None	Negative
30	F	19	5Y	Partial seizure	None	14	Maculopapular erythema	None	Positive

Table 3
Frequencies of HLA alleles and their relations to OXC-induced cADRs.

HLA alleles	Frequency (%)		OR (95% CI)	p value
	OXC-induced cADRs(2n = 60)		OXC-tolerant(2n = 180)	
HLA-A*3201	4/60(6.5)	0/180(0)	15.877 (1.817-138.720)	0.00*
HLA-B*1502	0/60(0)	11/180(6.1)	0.232 (0.030-1.824)	0.193

* $p < 0.05$(two-sided) was statistically significant.

allele may be more susceptible to OXC-induced cADRs. The HLA-A*3201 allele in Han population was particularly low. A recent research involving 8333 Chinese Han from Zhejiang Province, an eastern province of China, showed that the frequency of the HLA-A*3201 was 0.55%. [50]. The frequency of HLA-A*3201 was 1.11% in 90 Chinese Han from Beijing in the 1000 Genomes Dataset [51] and less than 1% in 1012 Chinese Han from Hubei Province, a middle part of China [52]. Thus, we propose that screening for HLA-A*3201 allele should be routinely conducted when considering administration of OXCs initially or in the face of AEDs adjustment.

As we know, the usual recommendation in the face of allergic reactions to AEDs is to abstain from use of the sensitizing drug because it can cause severe cADRs in some cases. Recently, several studies have shown that an alternative strategy is to desensitize patients who had to terminate OXC treatment because of mild cADRs despite receiving an advantageous treatment effect. If there is no better alternative medicine as a substitute, drug desensitization can be carefully considered in cases in which the benefit of desensitization is determined to be greater than the risk [53,54]. In our study, the median interval from initial administration to the allergic dose of OXC was found to be 6.43 ± 5.48 days (range 1-20 days), and the median latency of OXC-induced cADRs was 11.33 ± 5.18 days (range 2-23 days). Thus, all of the clinical events occurred within the first month of OXC use regardless of whether or not the initial dose was higher than 450 mg/day. According to the latest study of drug desensitization to OXC [55], the starting dosage during OXC desensitization was 0.1 mg/day, and then the dosage was increased gradually. The time spent in achieving the optimal dose of 10 mg kg^{-1}·day^{-1} was 63.6 ± 24.1 days (range 37-124 days), and the time taken to achieve the maximum therapeutic dosage was 116.0 ± 8.2 days (range 47-300 days). The long-term efficacy of OXC desensitization was satisfactory, manifested by favorable response and retention rates of more than 70% and 80% respectively, which can inspire the clinicians to apply the desensitization of OXC as an alternative therapeutic method for patients who are hypersensitive to OXC or have experienced mild cADRs.

Cross-sensitivity between AEDs was also demonstrated in this study, as one patient had a history of a lamotrigine (LTG)-associated rash in OXC-induced MPE. This suggests that history of another AED rash could be a predictor of OXC-related MPE and a risk factor for developing a rash in response to OXC. Therefore, if a patient has a history of a medicine allergy, particularly to aromatic AEDs such as PHT, CBZ, and LTG, a prescription for OXC needs to be carefully considered. Other predictors of OXC allergy remain unclear. One study showed that women were significantly more likely to develop a drug allergy than men [56], although we did not find a significant difference in age, sex, or history of allergy between OXC-tolerant and OXC-cADR patients. The same association has also been observed in previous studies examining patients taking LTG [57] or OXC [11].

5. Conclusion

In this case-control association study, we demonstrated that HLA-A*3201, and not HLA-B*1502, confers greater susceptibility to OXC-induced cADRs in the Chinese Han population, indicating that screening for this allele should be conducted before OXC application. Despite the fact that we recruited the greatest number of Eastern Chinese patients among all genetic association studies of OXC-induced cADRs conducted to date, the definitive associations of OXC-induced cADRs with HLA alleles warrant further study.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2018.12.011.

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