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HLA-B*1502 is associated with aromatic anticonvulsant drug-induced cutaneous adverse drug reactions among the Hakka population in China

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Abstract

Background: The purpose of this study was to analyze the correlation between aromatic antiepileptic drug-induced cutaneous adverse drug reactions and HLA-B*1502 genotype in patients from the Hakka population in Meizhou.

Methods: A total of 214 epileptic patients taking aromatic (n = 94) or non-aromatic anticonvulsants (n = 120) were included in the study from September 2016 to May 2018.

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Clinical data for the patients were analyzed retrospectively and HLA-B*1502 genotype testing was carried out.

Results: Thirty patients were HLA-B*1502(+) (14.02%). The proportion of HLA-B*1502(−) genotype and incidence of adverse drug reactions (ADRs) differed significantly between the two drug groups. In the aromatic anticonvulsant group, maculopapular eruption (MPE), Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome (HSS) occurred in 10 patients, including eight HLA-B*1502(+) and two HLA-B*1502(−) patients. MPE, HSS, SJS, and TEN occurred in 26 patients in the non-aromatic anticonvulsant group, including one HLA-B*1502(+) and 25 HLA-B*1502(−) patients. There was a significant correlation between the proportions of HLA-B*1502(+) genotype and induced cutaneous adverse drug reactions in the two groups.

Conclusions: HLA-B*1502 is associated with aromatic anticonvulsant drug-induced cutaneous adverse drug reactions among the Hakka population in Meizhou, China.

Keywords

HLA-B*1502, antiepileptic, cutaneous adverse drug reaction, Hakka, aromatic anticonvulsant agent, genotype

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Introduction

Adverse drug reactions (ADRs) are defined by the World Health Organization as noxious and unintended responses to a drug at a dose that is normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for modifications of physiological function.[1] ADRs are a serious cause of morbidity and mortality worldwide and will continue to pose a threat to public health as long as drugs are used in clinical treatments.

Aromatic anticonvulsants are first-line antiepileptic drugs and emotional stabilizers. Aromatic antiepileptic drugs including carbamazepine, oxcarbazepine, phenytoin sodium, and lamotrigine are commonly used, mainly for the treatment of epilepsy and mania, but also for schizophrenia and trigeminal neuralgia. However, aromatic anticonvulsants are one of the most common causes of cutaneous ADRs (cADRs).[2] The incidence of ADRs that is associated with newly used carbamazepine is 1:1000–1:10,000 individuals.[3] The cADRs range from mild maculopapular eruption (MPE) to hypersensitivity syndrome (HSS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), based on increasing severity.[4,5] MPE is characterized by cutaneous fine pink macules and papules, and lesions that usually fade within 1 to 2 weeks following cessation of drug treatment. HSS is characterized by multi-organ involvement accompanied by systemic manifestations in addition to skin rashes, with skin manifestations of HSS that vary from MPE to exfoliative dermatitis. SJS and TEN are characterized by rapidly developing blistering exanthema that consist of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment.

The development of pharmacogenomics has led to an interest in the relationship between ADRs that are caused by some drugs and human leukocyte antigen

(HLA) gene polymorphisms. It is important to identify gene markers related to ADRs that are caused by aromatic anticonvulsants, with significant implications for clinical drug selection for epilepsy. Carbamazepine-induced SJS/TEN was shown to be closely related to the HLA-B*1502 gene in Hong Kong, Malaysia, Thailand, and India, as well as in ethnic groups from the South Pacific.[6–8] Studies in India, Thailand, and Malaysia reported multiple cases of carbamazepine-induced SJS/TEN in HLA-B*1502 genotype(−) individuals,[9–11] and other studies found a strong correlation between the HLA-A*31:01 genotype and SJS/TEN induced by carbamazepine in Japanese and white populations.[12,13]

Meizhou is located in eastern Guangdong Province, with a resident population of 5.28 million and an annual birth rate of 12.45% (based on the official web site of the Bureau of Health and Family Planning of Meizhou, China). Most Meizhou residents are Hakka people, belonging to an ethnically Han Chinese population that mainly inhabits southern China. The Hakka originated from a southern migration from the central plains in the north, and possess a unique genetic background.

There have been no previous reports of an association between HLA-B*1502 genotype and ADRs induced by aromatic anticonvulsant drugs in the Hakka population in Meizhou, China. This retrospective study, therefore, aimed to analyze the correlation between cADRs and HLA-B*1502 genotype in Hakka patients from Meizhou who had taken aromatic and non-aromatic antiepileptic drugs, to provide evidence for the individualized treatment of epilepsy.

Materials and methods

Subjects

We retrospectively collected the clinical histories and medication records of patients with epilepsy who were treated with aromatic or non-aromatic anticonvulsants at Meizhou People's Hospital (Huangtang Hospital) from September 2016 to May 2018. The patients were classified into two groups based on the use of aromatic or non-aromatic anticonvulsants. Aromatic anticonvulsant drugs included carbamazepine, phenytoin sodium, lamotrigine, oxcarbazepine, and phenobarbital. Non-aromatic anticonvulsant drugs included levetiracetam, topiramate, sodium valproate, and clonazepam.

Based on the clinical morphology defined by Roujeau,[14] SJS was defined as skin detachment on $< 10\%$ of the total body-surface area and TEN was defined as skin detachment on $> 30\%$. The criteria for HSS were skin rash together with fever, eosinophilia, and atypical lymphocytosis with involvement of at least one internal organ.

The flow chart for this study is shown in Figure 1. The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong, China. Written informed consent was obtained from all patients.

DNA extraction and genotyping

Peripheral blood was collected from all patients into EDTA anticoagulant tubes. Genomic DNA was extracted from the blood of subjects using a QIAamp DNA Blood Mini Kit (QAIGEN GmbH, Hilden, Germany), in accordance with the manufacturer's instructions. DNA concentration was quantified using a NanoDrop 2000^{TM} Spectrophotometer (Thermo Fisher Scientific, Rockford, IL, USA).

Polymerase chain reaction (PCR) to detect the HLA-B*1502 genotype was performed in accordance with the following protocol: pre-denaturation at 95°C for

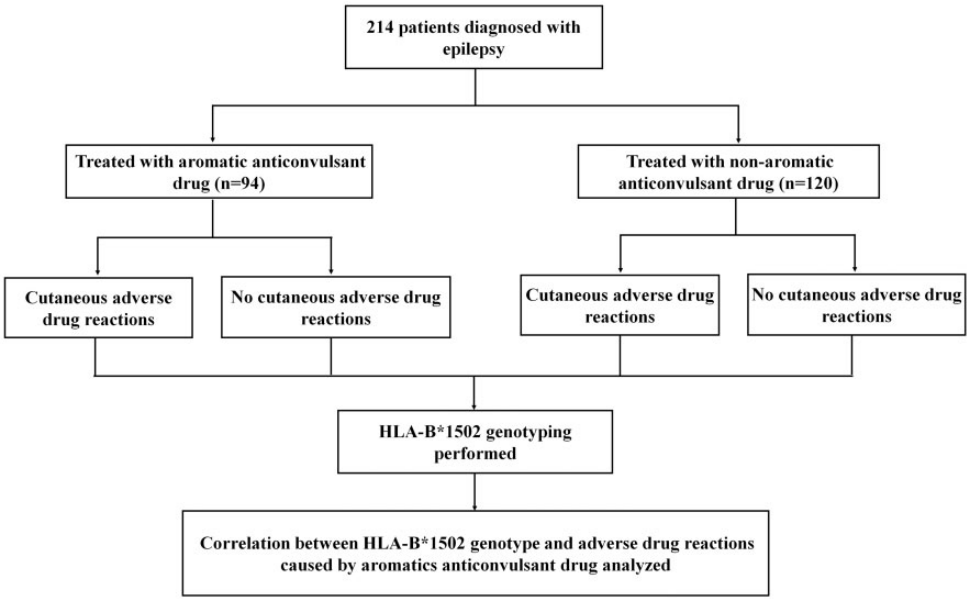

Figure 1. Flow chart for this study.

10 minutes, and then 35 cycles of amplification, 15 seconds at 95°C for denaturation, and 60 seconds at 71°C for elongation. The fluorescence signals were collected at 71°C each time. Melting curve analysis was performed at 95°C for 15 seconds and 65°C for 1 second. The results were analyzed based on Ct values and the $2^{-\Delta\Delta CT}$ value was calculated. Real-time PCR and analysis were performed using an HLA-B*1502 Detection Kit (Pharmigene, Inc., Taiwan, China), in accordance with the manufacturer's instructions.

Statistical analysis

SPSS Statistics for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The data were expressed as the mean ± standard deviation. Differences between the aromatic and non-aromatic anticonvulsant treatment groups were analyzed using χ^2 and ANOVA tests. A value of $P < 0.05$ was considered to be statistically significant.

Results

Population characteristics

Two hundred fourteen patients aged 8 to 92 years, including 131 men (61.21%, mean age 56.20 ± 18.93 years) and 83 women (38.79%, mean age 51.91 ± 19.54 years) (1.58:1), were recruited from September 2016 to May 2018 (Table 1). There was no significant difference in the age or sex ratio between the two groups. The clinical diagnoses of patients included epilepsy, trigeminal neuralgia, and affective disorders. Epilepsy was significantly more frequent among patients taking aromatic agents ($P < 0.001$) (Table 1).

*HLA-B*1502 genotypes and ADRs*

The genotypes of the patients and ADRs in relation to the type of drug used are shown in Table 2. The proportion of HLA-B*1502 (−) genotype ($P = 0.009$) and incidence of ADRs ($P = 0.042$) differed significantly

Table 1. Baseline clinical characteristics.

Variable	Aromatic anticonvulsant drug group (n = 94)	Non-aromatic anticonvulsant treatment group (n = 120)	*P* value
Age (years)	42.60 ± 20.68	47.62 ± 20.18	0.075
Sex			
Male	56 (59.57%)	75 (62.50%)	0.674 ($\chi^2 = 0.190$; OR = 0.884; 95% CI, 0.508–1.538)
Female	38 (40.42%)	45 (37.50%)	
Clinical diagnosis			
Epilepsy	80 (85.11%)	63 (52.50%)	<0.001 ($\chi^2 = 25.277$; OR = 5.170; 95% CI, 2.642–10.118)
Epileptiform neuralgia/other	14 (14.89%)	57 (47.50%)	

Age is expressed as the mean ± standard deviation. Aromatic anticonvulsant drugs included carbamazepine, phenytoin sodium, lamotrigine, oxcarbazepine, and phenobarbital. Non-aromatic anticonvulsant drugs included levetiracetam, topiramate, sodium valproate, and clonazepam. OR, odds ratio; CI, confidence interval.

Table 2. Incidence of HLA-B*1502 genotype and drug-induced cutaneous adverse drug reactions based on drug use.

	Aromatic anticonvulsant drug group (n = 94)	Non-aromatic anticonvulsant drug group (n = 120)	Total (n = 214)	*P* value
Group				
HLA-B*1502(+) (n,%)	20 (21.28)	10 (8.33)	30 (14.02)	0.009 ($\chi^2 = 7.326$; OR = 0.336; 95% CI, 0.149–0.759)
HLA-B*1502(−) (n,%)	74 (78.72)	110 (91.67)	184 (85.98)	
Drug-induced cADRs				
MPE (n,%)	1 (1.06)	6 (5.00)	7 (3.27)	0.645 ($\chi^2 = 0.788$; OR = 2.700; 95% CI, 0.282–25.834)
SJS (n,%)	5 (5.32)	11 (9.17)	16 (7.48)	0.722 ($\chi^2 = 0.173$; OR = 0.733; 95% CI, 0.170–3.169)
TEN (n,%)	3 (3.19)	4 (3.33)	7 (3.27)	0.370 ($\chi^2 = 0.985$; OR = 0.424; 95% CI, 0.076–2.373)
HSS (n,%)	1 (1.06)	5 (4.17)	6 (2.80)	0.655 ($\chi^2 = 0.443$; OR = 2.143; 95% CI, 0.218–21.047)
Total cADRs	10 (10.64)	26 (21.67)	36 (16.82)	0.042 ($\chi^2 = 4.582$; OR = 2.323; 95% CI, 1.058–5.101)

cADR, cutaneous adverse drug reaction; MPE, maculopapular exanthema, SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; HSS, hypersensitivity syndrome; OR, odds ratio; CI, confidence interval.

between the two groups. There were no significant differences in the incidence of MPE, SJS, TEN, and HSS between the two groups (Table 2).

cADRs occurred in 10 patients in the aromatic anticonvulsant drug group (8 HLA-B*1502(+), 2 HLA-B*1502(−)) and in 26 patients in the non-aromatic anticonvulsant drug group (1 HLA-B*1502(+), 25 HLA-B*1502(−)). The incidence of cADRs among HLA-B*1502(+) patients was significantly higher in patients taking

Table 3. Occurrence of cutaneous adverse drug reactions and the HLA-B*1502 genotypes based on drug use.

Group	HLA-B*1502(+)/ cADR(+) (n,%)	HLA-B*1502(+)/ cADR(−) (n,%)	HLA-B*1502(−)/ cADR(+) (n,%)	HLA-B*1502(−)/ cADR(−) (n,%)
Aromatic anticonvulsant (n = 94)	8 (8.51)	12 (12.77)	2 (2.13)	72 (76.60)
Non-aromatic anticonvulsant (n = 120)	1 (0.83)	9 (7.50)	25 (20.83)	85 (70.83)
Total (n = 214)	9 (4.21)	21 (9.81)	27 (12.62)	157 (73.36)
P value	0.011 ($\chi^2 = 7.712$; OR = 0.090; 95% CI, 0.011–0.736)	0.248 ($\chi^2 = 1.652$; OR = 0.554; 95% CI, 0.223–1.377)	<0.001 ($\chi^2 = 16.729$; OR = 12.105; 95% CI, 2.787–52.571)	0.355 ($\chi^2 = 0.896$; OR = 0.742; 95% CI, 0.400–1.378)

cADR, cutaneous adverse drug reaction; OR, odds ratio; CI, confidence interval.

Table 4. The 25 patients with HLA-B*1502(−) who had cutaneous adverse reactions.

cADR	Drug	HLA-B*1502(+)	HLA-B*1502(−)	HLA-B*5801(+)	HLA-B*5801(−)
MPE (n = 6)	Methimazole, propranolol, or Chinese herb	0	6	0	6
SJS (n = 11)	Allopurinol	0	11	9	2
TEN (n = 4)	Chinese herb	0	4	1	3
HHS (n = 4)	Unknown	–	–	–	–

cADR, cutaneous adverse drug reaction; MPE, maculopapular exanthema, SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; HSS, hypersensitivity syndrome.

aromatic agents ($P = 0.011$), while the incidence among HLA-B*1502(−) patients was significant higher among those taking non-aromatic agents ($P < 0.001$). There was no significant difference in the incidence of patients without cADRs between the two drug groups for either HLA-B*1502 genotype (Table 3).

*HLA-B*58:01 genotype and ADRs*

Twenty-five patients with HLA-B*1502(−) had cADRs, among whom 10 were HLA*5801(+). All these patients had used allopurinol. Other patients with cADRs were treated with methimazole, propranolol, or Chinese herbs (Table 4).

Discussion

Anticonvulsants are a group of drugs that are used to treat epileptic seizures. However, some patients have allergic reactions to these drugs. Several recent studies have shown that allergic reactions caused by carbamazepine are associated with *HLA* gene polymorphisms.[15–18] HLA-B*1502 is an *HLA* allele that is found almost exclusively in Asian populations, including Chinese Han, Filipinos, Malaysians, South Asian Indians, and

Thais, and it is estimated that at least 10% to 15% of epilepsy patients carry the HLA-B*1502 genotype.[19]

Allergic skin reactions include mild MPE,[20] HSS,[21] SJS, and TEN. Although SJS and TEN are potentially fatal cADRs, their pathogenesis is currently unclear, but it is usually related to the immune response. Researchers in Taiwan first reported a strong correlation between SJS/TEN and HLA-B*1502 in the Han population of Taiwan in 2004,[8] and the results of other studies have supported this finding. This correlation has been confirmed in the Chinese population and in other Asian countries.[9,11,22–24]

In the current study, the incidence of HLA-B*1502 genotypes and of ADRs differed significantly between patients taking aromatic and non-aromatic anticonvulsant drugs. HLA-B*1502 was associated with aromatic anticonvulsant drug-induced cADRs among the Hakka population in China. This supported the previous conclusion[22–24] that aromatic antiepileptic drug-induced cADRs were closely related to the HLA-B*1502 genotype. The results of this study suggest that clinicians should perform HLA-B*1502 genotyping before prescribing antiepileptic drugs for the treatment of epilepsy and other diseases. Aromatic drugs should be avoided in HLA-B*1502(+) patients to reduce the occurrence of serious ADRs such as SJS/TEN. Drug treatment must also be closely monitored.

In the present study, 25 HLA-B*1502(−) patients had cADRs, including 10 patients who were HLA*5801(+). A retrospective analysis revealed that these patients had used allopurinol, which is widely used for the prevention and treatment of hyperuricemia. Other studies have reported that allopurinol-induced cutaneous anaphylaxis was closely related to HLA-B*5801.[25–28] The HLA-B*5801 allele is, thus, strongly associated with severe allopurinol-induced cADRs. HLA-B*5801 and HLA-B*1502 genotypes are related to the responses to different types and dosages of drugs, and it is difficult to compare the effects of HLA-B*1502 and HLA-B*5801 on cADRs.

This study provides the first evidence for an association between HLA-B*1502 genotype and aromatic anticonvulsant drug-induced cADRs among the Hakka population in Meizhou, China. This study had some limitations, especially the relatively small number of subjects who had cADRs. Further studies with a larger sample size are planned to examine the relationship between the *HLA* allele (HLA-B*1502 and other genes) and various types of cADRs. Pharmacogenomics is an important study topic in our research group, and investigations into the association between gene variants and the efficacy and safety of anticonvulsants are ongoing, with the aim of providing better references for clinical applications.

Conclusions

HLA-B*1502 is associated with aromatic anticonvulsant drug-induced cADRs. HLA-B*1502 genotyping is, therefore, recommended in patients with epilepsy before medication, to prevent serious cADRs. This study provides the first evidence for an association between the HLA-B*1502 genotype and aromatic anticonvulsant drug-induced cADRs among the Hakka population in Meizhou. Pharmacogenomics studies to examine the association between gene variants and the efficacy and safety of anticonvulsants are ongoing, and further studies with a larger sample size are needed to provide more evidence for the clinical treatment of epilepsy.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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