

Association between *HLA* gene polymorphism and cutaneous adverse reactions caused by antiepileptic drugs

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Received August 16, 2017; Accepted January 15, 2018

DOI: 10.3892/etm.2018.5801

Abstract. The association between cutaneous adverse drug reactions (cADRs) caused by antiepileptic drugs (AEDs) and human leukocyte antigen-A (*HLA-A*) and *HLA-B* genes in Chinese Han population in Shanghai was investigated. Through the case-control study, 30 child patients with AED-induced cADRs (cADRs group), 60 AED-tolerant child patients (AED-tolerant group) and 60 normal children not taking AEDs (normal group) were collected. The *HLA-B*15:02* and *HLA-A*31:01* genotypes were detected using the polymerase chain reaction-sequence-specific oligonucleotide (PCR-SSO) probe method, and the correlation of *HLA-B*15:02* and *HLA-A*31:01* genes with the incidence of cADRs was analyzed. The positive rate of *HLA-B*15:02* gene was 83.33% in the cADRs group, which was significantly increased compared with that in the AED-tolerant and normal groups ($P<0.01$). The positive rate of *HLA-A*31:01* gene was 63.33% in the cADRs group, which was obviously increased compared with that in the AED-tolerant and normal groups ($P<0.01$). There were no significant differences in *HLA-B*15:02* and *HLA-A*31:01* genotypes between the AED-tolerant and normal groups ($P>0.05$). The results showed that *HLA-B*15:02* and *HLA-A*31:01* are significantly associated with cADRs in a Chinese Han population in Shanghai, suggesting that *HLA-B*15:02* and *HLA-A*31:01* genotypes should be detected in the application of AEDs.

Introduction

Epilepsy (EP) is a common neurological disease caused by abnormal brain cell super-synchronous discharge with the

main clinical features of repeated attack, transiency and stereotype (1), which occurs more frequently in children. There are approximately 10 million patients with epilepsy currently in China, and its incidence rate increases year by year with an annual increase of 450,000 individuals, seriously affecting the lives of patients (2).

At present, commonly used antiepileptic drugs (AEDs) in clinical practice include carbamazepine, phenytoin sodium, phenobarbital, lamotrigine, primidone and oxcarbazepine (3). There is a large difference in the blood concentration of AEDs in individuals, and adverse drug reactions often occur easily, the most common of which is the cutaneous adverse drug reaction (cADR) (4). The clinical manifestations of cADRs are maculopapule (MPE), Stevens-Johnson syndrome (SJS), drug hypersensitivity syndrome (HSS) and toxic epidermal necrolysis (TEN) (5,6). The incidence rates of SJS/TEN are lower (1:10000-6:10000 in European countries and 1:1000-6:1000 in Asian countries), but their fatality rates are extremely high (7), thus greatly limiting the clinical application of AEDs (8). In recent years, it has been shown that human leukocyte antigen (HLA) polymorphism has a significant correlation with the incidence of cADRs (9,10). However, other studies have found that some patients with negative HLA polymorphism also suffer from SJS/TEN (11,12).

In this study, the permanent population in Shanghai was taken as the subjects of study to investigate the correlation of *HLA-B*15:02* and *HLA-A*31:01* polymorphisms with the incidence of cADRs to identify the genetic factors leading to the cADRs.

Materials and methods

Subjects of study. Child patients treated or admitted to the Department of Neurology, Tianyou Hospital, Tongji University (Shanghai, China) from January, 2015 to January, 2017 were enrolled into the cADRs group ($n=30$). Child patients enrolled took AEDs for the first time and cADRs occurred within 8 weeks. Patients with other rashes similar to the drug rash were clearly eliminated via the consultation of dermatologists in our hospital. At the same time, 60 child patients treated or admitted to the Department of Neurology, Tianyou Hospital, Tongji University were randomly selected as the AED-tolerant

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Key words: antiepileptic drugs, cutaneous adverse reactions, *HLA-B*15:02*, *HLA-A*31:01*

Table I. PCR reaction parameters.

Step	Temperature (°C)	Time	Cycle
1	96	3 min	1
2	96	20 sec	5
	60	20 sec	
	72	20 sec	
3	96	10 sec	30
	60	15 sec	
	72	20 sec	
4	72	10 min	1

group. This group was administered AEDs for the first time and cADRs did not occur within 8 weeks. Normal children who did not take AEDs were randomly selected as the normal control group. The diagnosis of epileptic children was based on the international general diagnostic criteria (13): i) recurrent convulsion without obvious predisposing causes, and without concurrent infection, hyperpyrexia and other clinical manifestations; ii) EEG examination for child patients indicates an abnormal EEG; iii) all child patients take single AEDs without combined medication. There was no significant difference in the drugs used for child patients between the cADRs and AED-tolerant groups. The child patients and their parents were a permanent Han population in Shanghai.

This experiment was approved by the Ethics Committee of Tianyou Hospital (Shandong, China) and family members of child patients signed the informed consent.

Materials and instruments. Median whole blood genomic DNA extraction kit (Beijing BioTeke Corp., Beijing, China); HLA-SSO genotyping kit (One Lambda Inc., Canoga Park, CA, USA); ultramicro ultraviolet spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA); PCR amplifier (Applied Biosystems, Foster City, CA, USA); and a flow fluorescence detector (Luminex, Austin, TX, USA) were used in the present study.

Research methods

DNA extraction. DNA was extracted using the median whole blood genomic DNA extraction kit according to the protocol. The purity and concentration of DNA were detected using the Nanodrop-2000 ultramicro ultraviolet spectrophotometer, and the purity and concentration of the DNA samples met the experimental requirements.

PCR amplification. DNA sample (1 μ l) at a concentration of 20–40 ng/ μ l was taken and added with the substrate, primer and Taq mixture according to the protocol, and vibrated evenly, followed by PCR amplification. The specific reaction parameters are shown in Table I. The amplification products obtained received 2% agarose gel electrophoresis to determine the relevant DNA fragments.

Sample hybridization. Amplified DNA (5 μ l) was taken and added with an appropriate number of magnetic beads and

Table II. Comparison of general data.

Group	n	Male/female (n)	Age (years)
cADR	30	22/8	10.26 \pm 2.33
AED-tolerant	60	42/18	9.72 \pm 2.81
Normal	60	45/15	10.95 \pm 2.54

magnetic bead buffer, vibrated evenly and then incubated on the PCR amplification instrument at 60°C for 15 min. The mixture was washed with 50 μ l washing liquid 3 times, added with 25 μ l fluorescent liquid and incubated at 60°C for 5 min. After being washed again 3 times, the samples were read on Hoefer DQ 200 flow fluorometer (Hoefer, Inc., Piscataway, NJ, USA).

Statistical methods. SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data are presented as mean \pm SD, and one-way analysis of variance was used for the comparison among groups. Tukey test was used as post hoc test. *HLA* gene frequency in each group was calculated using the direct counting method. Chi-square test or Fisher's exact test was used for the comparison of *HLA* gene frequency in each group. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of general data. In the cADRs group, there were 9 child patients with SJS, 4 child patients with TEN, 6 child patients with HSS and 11 child patients with MPE. There were no significant differences in sex ratio and age among the three groups of children (Table II).

Comparison of *HLA-B*15:02* gene frequency in each group. The pairwise comparison was made for *HLA-B*15:02* gene frequency in child patients in the three groups. The results showed that the positive rate of *HLA-B*15:02* gene in the cADRs group was significantly higher than that in the AED-tolerant and normal groups, and the differences were statistically significant [$P < 0.001$, odds ratio (OR)=7.143, 95% confidence interval (CI)=3.496–14.593; $P < 0.001$, OR=25.00, 95% CI=6.34–98.578]. There was no statistically significant difference between AED-tolerant group and normal group ($P > 0.05$) (Tables III–V).

Comparison of *HLA-A*31:01* gene frequency in each group. The pairwise comparison was carried out for the *HLA-A*31:01* gene frequency in child patients for the three groups. The results showed that the positive rate of *HLA-A*31:01* gene in the cADRs group was significantly higher than that in the AED-tolerant and normal groups, and the differences were statistically significant ($P < 0.001$, OR=2.235, 95% CI=1.375–3.634; $P < 0.001$, OR=4.222, 95% CI=2.18–8.177). There was no statistically significant difference between the AED-tolerant and normal groups ($P > 0.05$) (Tables VI–VIII).

Table III. Comparison of *HLA-B*15:02* gene frequency between the cARD and AED-tolerant groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
cARD	25	5	83.33	46.886	<0.001
AED-tolerant	7	53	11.67		

Table IV. Comparison of *HLA-B*15:02* gene frequency between the cARD and normal groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
cARD	25	5	83.33	65.385	<0.001
Normal	2	58	3.33		

Table V. Comparison of *HLA-B*15:02* gene frequency between the AED-tolerant and normal groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
AED-tolerant	7	53	11.67	3.003	0.083
Normal	2	58	3.33		

Discussion

cADR is the delayed-type hypersensitivity mediated by immune mechanisms, whose incidence is associated with sex, age, region, initial dose of AEDs and history of allergy (8). In addition, its incidence is unpredictable and heterogeneous (14). MPE is the most common AED-induced cADR, and its main clinical manifestations are pink small papules and maculae on skin without involving the mucosa or organs, which can gradually disappear after drug withdrawal (15). The clinical manifestations of HSS, in addition to rash, are accompanied with multi-organ involvement and eosinophilia, while those of SJS and TEN are blister-like rash on skin, involving mucosal and multiple organs, accompanied with systemic excoriation. Excoriation of less than 10% indicates SJS, excoriation of greater than 30% indicates TEN, and excoriation between 10 and 30% indicates SJS/TEN overlap (5). The mortality rate of TEN is as high as 30-50% (16). It has been found that male patients are more likely to suffer from serious cADRs than female patients (17), and cADRs occur more easily in infants and the elderly (18). The incidence rate of cADRs varies from country to country: it is 6.60% in Japan, 5.88% in Australia, 27.70% in Singapore, 19.00% in India, 35.70% in Malaysia and 26.00% in Taiwan (19). It can be seen that the genetic specificity has an important influence on the occurrence of cADRs.

Studies have confirmed that *HLA* gene is closely related to serious cADRs induced by a variety of drugs. For example,

Table VI. Comparison of *HLA-A*31:01* gene frequency between the cARD and AED-tolerant groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
cARD	19	11	63.33	10.184	0.001
AED-tolerant	17	43	28.33		

Table VII. Comparison of *HLA-A*31:01* gene frequency between the cARD and normal groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
cARD	19	11	63.33	21.223	<0.001
Normal	9	51	15.00		

Table VIII. Comparison of *HLA-A*31:01* gene frequency between the AED-tolerant and normal groups.

Group	Gene			χ^2 test	P-value
	Positive	Negative	frequency (%)		
AED-tolerant	17	43	28.33	3.184	0.074
Normal	9	51	15.00		

*HLA-B*58:01* is a susceptibility gene for serious cADRs caused by allopurinol, and *HLA-B*57:01* is a susceptible gene for serious cADRs caused by Abacavir (20). Determining the susceptibility genes of drug-induced cADRs in the clinic can provide a genetic basis for the prevention of cADRs, which is a great progress in drug gene genetics. The *HLA* gene is located in the 21.31 region of the short arm of human chromosome 6, which has obvious genetic characteristics, and its encoded protein is closely related to the immune rejection after organ transplantation (10). *HLA* is divided into class I, II and III genes according to the different functions and locations of encoded molecule, of which *HLA-A*, *B* and *C* belong to class I genes (9). In recent years, a large number of studies have confirmed that *HLA* gene has a significant correlation with AED-induced cADRs, and patients carrying the *HLA* susceptibility gene are prone to cADRs (9,10).

*HLA-B*15:02* locus is studied the most currently. It was found for the first time in 2004 that *HLA-B*15:02* is significantly associated with carbamazepine-induced SJS in a Chinese Han population in Taiwan (21). Subsequently, it was confirmed that *HLA-B*15:02* is closely associated with carbamazepine-induced SJS/TEN in different ethnic groups in South Asia, such as Thailand, Malaysia, India and Vietnam (22-25). Further studies in Han population found that the correlation of *HLA-B*15:02* is related to the degree of skin peeling in SJS/TEN (26). The correlation between *HLA-B*15:02* and cADRs has an obvious race specificity, and it is not found in Japanese and European populations. It is speculated that it is related to

the very low distribution frequency of *HLA-B*15:02* in these populations (7,27). However, the distribution frequencies of *HLA-B*15:02* in China, Indian and Philippines are as high as 8, 21 and 34%, respectively (20,25). The present findings have shown that *HLA-B*15:02* is a risk factor for carbamazepine-induced cADRs in the Asian population. The present findings have also confirmed that *HLA-B*15:02* was strongly associated with AED-induced cADRs in Han population in Shanghai, which was consistent with the study on Han population in other areas of China. Thus, now it is recommended by many regulators that *HLA-B*15:02* genotyping be performed before administration of carbamazepine and other AEDs, thereby reducing the incidence of cADRs (22,25,28).

*HLA-A*31:01* is another genotype that is closely related to AED-induced cADRs. The distribution frequencies of *HLA-A*31:01* in Chinese Han population, Japanese, Korean and Caucasian population are 2.2, 9.3, 5 and 4.2%, respectively. However, its distribution frequency was as low as 0.01% in an African population (29). A number of studies in Japanese and European populations have shown that *HLA-A*31:01* is strongly associated with AED-induced cADRs (27,30). Genin *et al* (31) found in meta-analysis in different ethnic groups that *HLA-A*31:01* is significantly associated with the carbamazepine-induced HSS (OR=13.2, 95% CI=8-20.8), indicating that *HLA-A*31:01* is a specific susceptibility gene for carbamazepine-induced HSS. Another meta-analysis found that (32) the specificity of *HLA-A*31:01* was 0.871-0.972, the sensitivity was 0.262-0.584, the negative predictive value was 0.921-0.986 and the positive predictive value was 0.119-0.427 in the prediction of cADRs via *HLA-A*31:01* gene screening in Han population in Japan, Europe and China (32). Therefore, it is recommended by Canada Pharmacogenomics Safety Network that *HLA-A*31:01* gene screening be performed for patients before the application of carbamazepine, and carbamazepine be avoided for genetically positive patients (25). The present study also confirmed that *HLA-A*31:01* has a significant correlation with the AED-induced cADRs in a Han population in Shanghai, which is consistent with the result in previous cohort studies. Therefore, *HLA-A*31:01* gene screening prior to the administration of AEDs plays an important role in the prevention of cADRs.

In conclusion, it was confirmed in the present study that *HLA-B*15:02* and *HLA-A*31:01* are significantly associated with cADRs in Chinese Han population in Shanghai, and *HLA-B*15:02* and *HLA-A*31:01* gene screening prior to the administration of AEDs can prevent the occurrence of cADRs. In this study, the sample size was small, and it was a mixed study on a number of AEDs; thus, the sample size should be increased, and the control study on single drug and the interaction research among multiple genes are needed in the future. This study only aimed at a single *HLA* gene. As such, other relevant risk or protective factors remain to be further studied.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Author's contributions

YH contributed to the conception of the study. JZ contributed significantly to analysis and manuscript preparation. XL performed the data analyses and wrote the manuscript. YS, MS and JW helped perform the analysis with constructive discussions.

Ethics approval and consent to participate

This experiment was approved by the Ethics Committee of Tianyou Hospital and family members of child patients signed the informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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