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Carbamazepine- but not phenytoin-induced severe cutaneous adverse drug reactions are associated with *HLA-B*1502* in a Thai population

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Abstract

Antiepileptic drugs (AED) containing aromatic rings such as carbamazepine (CBZ) and phenytoin (PHT) have been reported as the most common culprit drug for severe cutaneous adverse drug reactions (SCADR) in several Asian countries including Thailand. A strong association between *HLA-B*1502* and CBZ-induced SJS/TEN has been reported in Han Chinese but not in Caucasian and Japanese populations. A case-control study was therefore conducted to determine whether *HLA-B*1502* is a valid pharmacogenetic test for SCADR caused by CBZ and PHT in a Thai population.

Among 49 CBZ-induced SCADR patients, 45 (89.58%) patients carried the *HLA-B*1502* while only 5 (10.42%) of the CBZ-tolerant controls had this allele. The risk of CBZ-induced SCADR was significantly higher in the patients with *HLA-B*1502* with an odds ratio (OR) of 74 (95%CI 17–341, $p < 0.001$). Among the 18 PHT-induced SCADR patients, the *HLA-B*1502* allele was present in only 5 (27.8%) of these patients, whereas 7 (19.4%) of the PHT-tolerant controls carried this allele. The risk of PHT-induced SCADR was not significantly higher in the patients with *HLA-B*1502* (OR= 1.6; 95%CI 0.3-7.1, $p = 0.50$). Results from this study suggest that *HLA-B*1502* is a good marker for CBZ-induced SCADR but not for PHT-induced SCADR in a Thai population.

Keywords: *HLA-B*1502*, carbamazepine, phenytoin, severe cutaneous adverse drug reactions (SCADR)

Introduction

Antiepileptic drugs (AED) containing aromatic rings such as carbamazepine (CBZ) and phenytoin (PHT) are the most common culprit drugs of severe cutaneous adverse drug reactions (SCADR). These SCADR include hypersensitivity syndrome (HSS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1].

Although the pathogenesis of SCADR is not fully understood but there is some evidence that genetic may plays importance role [2]. Recent studies in Han Chinese and Thais showed that the *HLA-B*1502* allele is strongly associated with CBZ and this allele may also associated with PHT-induced SJS/TEN [3-5]. In contrast, the association between *HLA-B*1502* and CBZ- and PHT-induced SJS/TEN could not be demonstrated in Caucasian and Japanese populations[6].

Given the serious and life-threatening consequences of SJS/TEN and its extremely strong association with *HLA-B*1502*, the US-FDA has recently released a warning to health professionals and patients that these SCADR may occur in patients with *HLA-B*1502* and has also recommended genetic screening for patients of Asian ancestry prior to initiation of CBZ or PHT therapy. It should be noted that the FDA alert is not specific about the

definition of Asian [7]. In fact, the frequency of *HLA-B*1502* allele among Asian populations are vary, ranging from 10–15% in Han Chinese and South East-Asian populations to less than 1% in Japanese, Koreans [6, 7]. It should also be noted that the prevalence of CBZ-and PHT-induced SJS/TEN is positively correlated with the frequency of *HLA-B*1502* in different populations [8]. The objectives of this study were to determine the association between the *HLA-B*1502* allele and CBZ-and PHT-induced SCADR in a Thai population.

Materials and Methods

Study design: The retrospective case–control study was conducted in 10 local hospitals in Thailand.

Patients: CBZ and PHT-induced SCADR were identified from their medical records. The diagnosis of SCADR were confirmed by either a dermatologist or an internist based on the clinical morphology of the patients' skin according to Roujeau *et al.* [1]. CBZ and PHT were identified as the culprit drug if the symptoms occurred within the first 3 months of exposure and the symptoms resolved upon withdrawal of this drug. Patients who had used CBZ/PHT for ≥ 6 months without evidence of any cutaneous reactions were recruited as controls. Subjects were informed both verbally and in writing about the experimental procedures and the purpose of the study. The study protocol was approved by the institutional review boards.

***HLA-B*1502* genotyping:** Analysis for the presence of the *HLA-B*1502* allele was performed using a PG1502 DNA detection kit (PharmiGene, Inc., Taipei, Taiwan).

Statistical analysis: Data are expressed as positive or negative for *HLA-B*1502*. Chi-square test and Fisher's exact test were used to analyze the association between AED-induced SCADR and *HLA-B*1502* status. *P*-values ≤ 0.05 (two-sided) were considered statistically significant.

Results

Forty-eight patients who had been diagnosed with CBZ-induced SJS/TEN and 48 patients who received CBZ for at least 6 months without any evidence of cutaneous reactions were enrolled as cases and controls. Whereas eighteen patients who had been diagnosed with PHT-induced SCADR and 36 patients who received PHT for at least 6 months without any evidence of any cutaneous reactions were enrolled as cases and controls.

Among CBZ-patients, the *HLA-B*1502* allele was present in 43/48 (89.6%) of CBZ-induced SJS/TEN patients, whereas only 5/48 (10.4%) of the CBZ-tolerant controls carried this allele. The risk of CBZ-induced SJS/TEN was significantly higher in the patients with *HLA-B*1502* with OR of 74 (95% CI 17 – 341, $p < 0.001$).

Among PHT-patients, the *HLA-B*1502* allele was present in only 5/18 (27.8%) of PHT-induced SCADR patients, whereas 7/36 (19.4%) of the PHT-tolerant controls carried this allele. The risk of PHT-induced SCAR was not significantly higher in the patients with *HLA-B*1502* (OR = 1.6 ; 95% CI 0.3-7.1, $p = 0.50$).

Table 1. Risk of CBZ-induced SJS/TEN in patients with *HLA-B*1502* compare to CBZ-tolerant controls

<i>HLA-B*1502</i>	Number of patient SJS/TEN	Tolerant control	Odds ratio (95%CI)	<i>P</i> value
Positive	43(89.58%)	5(10.42%)	73.96	<0.001
Negative	5(10.42%)	43(89.58%)	[17.46-340.70]	
Total number	48	48		

Table 2. Risk of PHT-induced SCADR in patient with *HLA-B*1502* compare to PHT-tolerant control

<i>HLA-B*1502</i>	Number of patient SJS/TEN	Tolerant control	Odds ratio (95%CI)	<i>P</i> value
Positive	5(27.78%)	7(19.44%)	1.59	0.50
Negative	13(72.22%)	29(80.56%)	[0.32-7.13]	
Total number	18	36		

Conclusion

Consistence with those reports in Han Chinese and Thai epileptic patients, strong association between *HLA-B*1502* and CBZ-induced SJS/TEN was observed in the present study. The use of *HLA-B*1502* as a screening test before prescribing CBZ will help to prevent CBZ-induced SJS/TEN in Thailand.

Based on the fact that there is a strong association of the *HLA-B*1502* and CBZ-induced SJS/TEN and the structure of PHT is very similar to CBZ, the FDA promptly alert the physicians and patients to aware of the genetic link between *HLA-B*1502* and PHT-induced SJS/TEN. Although recent studies reported a high frequency of *HLA-B*1502* in PHT-induced SJS/TEN in Han Chinese and Thai epileptic patients, the number of reported cases were very small (only 1 Chinese and 4 Thais) [5, 9]. Results from our study reveal that the risk of PHT-induced SCAR was not significantly higher in the patients with *HLA-B*1502*. This lack of association between *HLA-B*1502* and PHT-induced SCADR may suggest that the *HLA-B*1502* screening test not be so useful for prediction of PHT-induced SCADR. However, larger number of patients may need to be confirmed about the lack of this association.

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