Genetic susceptibility and pharmacogenomics of severe cutaneous adverse drug reactions

Yuan-Tsong Chen¹, ²

¹ Institute of Biomedical Sciences, Academia Sinica, 128, Academia Road, Section 2. Nankang, Taipei, Taiwan
² Department of Pediatrics, Duke University Medical Center, Durham NC, USA

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Summary

Several recent studies have reported strong genetic associations between HLA-B and susceptibility to drug hypersensitivity. The genetic associations are often drug-specific; HLA-B*1502 is associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), HLA-B*5701 with abacavir hypersensitivity, and HLA-B*5801 with allopurinol-induced severe cutaneous adverse reactions. The genetic association can also be phenotype-specific; B*1502 is associated solely with carbamazepine-SJS/TEN, and not with either maculopapular eruption or hypersensitivity syndrome. Furthermore, genetic association can be ethnicity-specific; carbamazepine-SJS/TEN associated with B*1502 is seen in Southeast Asians but not in Caucasians or Japanese, which can be explained by the difference in allele frequencies among populations. The strong genetic association suggests a direct involvement of HLA in the pathogenesis of drug hypersensitivity, in which the HLA molecule presents an antigenic drug for T-cell
activation. Pharmacogenomic study has identified an unusual form of granulysin secreted by cytotoxic T lymphocytes and natural killer cells responsible for the disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. The high sensitivity/specificity of some of these genetic markers provides a plausible basis for developing tests to identify individuals at risk for these life-threatening conditions in some populations. Application of HLA-B*1502 and HLA-B*5701 genotyping as a screening tool for patients taking carbamazepine and abacavir, respectively, has reduced the incidence of these adverse drug reactions.

Introduction

Adverse drug reactions (ADRs) account for 6-7% of all hospital admissions and remain a major clinical problem. [1]. Clinically, ADRs are commonly classified into two types: type A and type B [2]. Type A reactions are predictable from the known pharmacology of the drug and often dose-dependent. By contrast, type B reactions are historically referred to as being unpredictable, polygenic and dose-independent idiosyncratic reactions. However, we now know that some of these reactions are in fact predictable and probably represent MHC-mediated responses to a drug modified antigen.

Among the many type B ADRs that have cutaneous manifestations characterized by skin rashes, Stevens-Johnson syndrome (SJS) and its related disease toxic epidermal necrolysis (TEN) are the most serious and life-threatening [3]. SJS is characterized by high fever, malaise, and a rapidly developing blistering exanthema of macules and target-like lesions accompanied by mucosal involvement. TEN has similar presentations with an even more extensive skin detachment and a higher mortality rate (30–40%) [4]. Although the incidence of SJS/TEN is low, these conditions can kill or severely disable previously otherwise healthy people. A few cases have prompted the pharmaceutical companies’ withdrawal of newly released drugs [4].

Incidence of SJS/TEN and common causative drugs vary between countries

The incidence of SJS/TEN varies from country to country. In Western countries, the incidence of TEN is 0.4-1.2 cases per million person-years and that of SJS 1-6 cases per million person-years [5, 6]. In Han Chinese, the estimated incidence of SJS is estimated to be 8 cases per million person-years (which is higher than that in Western countries) [7]. The common causative drugs also vary from country to country [8]. In Western countries, the most common causes of SJS/TEN are sulfonamides and NSAIDs, followed by phenobarbital and aminopenicillins; and more recently allopurinol has become the leading culprit drug in Europe. However, in South-East Asia including Taiwan, carbamazepine (CBZ) is the single most commonly offending drug associated with SJS/TEN, accounting for 26-35% of all cases. Phenobarbital or sulfonamides-induced SJS/TEN is relatively rare in countries of South-East Asia [8].
Association of HLA-B*1502 with CBZ-SJS/TEN

We previously studied the genetic polymorphisms of cytochrome P450 single nucleotide polymorphisms (SNPs) and genes involved in immune-related function in 44 patients with CBZ-SJS (including 5 with overlapping TEN) and compared their allele frequencies with 101 tolerant controls [7]. We found that all 44 patients (100%) who developed CBZ-SJS/TEN carried the HLA-B*1502 allele, while only 3% of the CBZ-tolerant group (corrected P value <0.001), and 8.6% of 93 health subjects (corrected P value <0.001) carried the allele. In addition, alleles Cw*0801, DRB1*1202, and A*1101 also occurred at significantly increased frequencies among the CBZ-SJS/TEN patients compared to the CBZ-tolerant controls or the general population. These closely linked alleles formed the HLA-B*1502 extended haplotype as HLA-A*1101-Cw*0801-B*1502-DRB1*1202.

The tight association of HLA-B*1502 with CBZ-SJS/TEN was further confirmed in our extended study group of now close to one hundred CBZ-SJS/TEN patients, and has also been confirmed in other Southeast Asian populations/countries where the allele is prevalent [9-13]. These patients were from widely separated geographic areas (Taiwan, Hong Kong, China, Australia, Europe and United States); however, all patients identified were Southeast Asians or Asian descendants. In contrast, no HLA-B*1502 association was found in Japanese and Caucasians [13, 14].

We also investigated whether HLA-B*1502 is associated with other cutaneous ADRs caused by CBZ, such as maculopapular exanthema and hypersensitivity syndrome (HSS). However, none of them showed significant association with HLA-B*1502, suggesting that the genetic association between HLA-B*1502 and CBZ-SJS/TEN is specific to SJS and TEN (9).

Association of HLA-B*1502 with other antiepileptic drugs-induced - SJS/TEN

We also extended the study of HLA susceptibility to 3 different antiepileptic drugs (AEDs), phenytoin (PHT), lamotrigine (LTG) and oxcarbazepine (OXC), having structure similarity to CBZ. We found that HLA-B*1502 was present in 8 of 26 (30.8%) PHT-SJS/TEN, 2 of 6 LTG-SJS, and 3 of 3 OXC-SJS patients [15]. Our results indicate that OXC, PHT and LTG, which possess an aromatic ring as CBZ, when causing SJS/TEN, shared common risk allele. We suggest that other aromatic AEDs including OXC, PHT and perhaps LTG should be used with caution in individuals tested positive for B*1502.

Association of HLA-B alleles with cutaneous ADRs caused by other drugs

Besides CBZ-SJS/TEN, there are other examples of associations between HLA-B alleles and severe cutaneous ADRs caused by drugs. Previous studies have shown weak associations of HLA-A29, B12, and DR7 with
sulfonamide-related SJS/TEN; A2 and B12 with oxicam-related SJS/TEN; B59 with SJS plus ocular involvement; and AW33 and B17/BW58 with allopurinol-induced drug eruption. The apparent weakness of the predictive value of these older markers could be due to differences in patient ascertainment, lack of phenotypic or diagnostic precision, and/or lack of a precise genotyping method for HLA allele subtypes at that time. Diagnosing SJS/TEN accurately, separating them from other adverse reactions, and identifying the culprit drug are critical factors for the success of these genetic studies.

More recently, hypersensitivity to abacavir, an antiretroviral drug for HIV infection, has been reported to be associated with another HLA-B allele (B*5701) [16], and allopurinol-induced severe cutaneous ADRs including SJS/TEN have been reported to be tightly associated with HLA-B*5801 (odds ratio 580) (17). Taken together, these studies suggest that HLA-B alleles and other genetic polymorphisms in the MHC region might play a major role in the pathogenesis of immune-mediated severe cutaneous ADRs.

Working model of the pathogenesis of drug-induced SJS/TEN

The strong association between the HLA-B molecules and severe cutaneous ADRs implies that these two events may be more than simply an allele in linkage disequilibrium with the polymorphism(s) mediating the functional effect. The tight association may reflect the direct functional involvement of HLA-B molecules in the pathogenesis of the disease. A working model in which the HLA-B*1502 allele may participate in the initiation of CBZ-SJS/TEN-related immune reactions has been proposed [8]. In this model, CBZ or its metabolites bind to peptide that is complexed with the HLA-B*1502 molecule and displayed on the cell surface of keratinocytes, and/or other antigen presenting cells (APC). Naïve CD8+ T lymphocytes with specific T cell receptors are activated by professional APCs in the lymph node. Upon the formation of immunological synapse and the signaling of costimulatory molecules, the drug-specific T cells proliferate and differentiate into effector cells to initiate the immune reactions to CBZ or its metabolites. This would then result in activation of cytotoxic T cells and initiate the apoptotic pathway that leads to necrosis of the epidermis. We have now identified a 15 kDa precursor form of granulysin, secreted by activated cytotoxic T cells and natural killer T cells, as the key molecule responsible for the disseminated keratinocyte death in SJS/TEN [18].

HLA B*1502 allele frequency positively correlates with prevalence of CBZ-SJS/TEN in different populations

Table 1 summarizes the allele frequency of HLA-B*1502 in different ethnic populations. B*1502 allele is present at a higher frequency in countries of South-East Asia than in countries of North-East Asia, Europe, Africa and America. The allele frequency of HLA-B*1502 is ~2-7% in Southern Han Chinese, but only 0-0.3% in Japanese and 0-0.1% in
Caucasians. The low frequency of B*1502 in Japanese and Caucasians may explain the apparent lower incidence of CBZ-SJS in these populations. Interestingly, HLA-B*1502 allele is quite common in Malaysia (8.4%), and CBZ is reported to be the major offending drug for SJS/TEN in that population (35.7% of SJS/TEN patients) (Table 1). The allele frequency of B*1502 has a positive relationship with the prevalence of CBZ-SJS/TEN in different ethnic groups.

**HLA-B*1502 as a test to identify individuals at risk for CBZ-induced SJS/TEN**

Preventing severe adverse drug reactions by screening out people at risk using a simple genetic test is a goal of many pharmacogenomic studies. However, before the test can be used in clinical practice, several important issues need to be considered. These include the incidence and severity of the adverse event, the sensitivity and specificity of the predictive marker, and whether equally effective alternative medications are available for individuals who test positive.

In using HLA-B*1502 allele as a test to identify the high risk patients, the test should have 98.3% sensitivity and 95.8% specificity. Assuming 0.25% prevalence rate, the presence of B*1502 has a 5.6% positive predictive value for detecting CBZ-SJS/TEN, whereas its absence has a 99.9% negative predictive value. The ratio of the odds in test positive

<table>
<thead>
<tr>
<th>Ethnic population</th>
<th>HLA-B*1502</th>
<th>Ethnic population</th>
<th>HLA-B*1502</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han Chinese (Taiwan)*</td>
<td>2.7-5.9%</td>
<td>China North Han</td>
<td>1.9%</td>
</tr>
<tr>
<td>Thailand*</td>
<td>8.5%</td>
<td>China South Han</td>
<td>7.1%</td>
</tr>
<tr>
<td>Singapore*</td>
<td>5.7%</td>
<td>US Caucasian</td>
<td>0-1%</td>
</tr>
<tr>
<td>Malaysia*</td>
<td>8.4%</td>
<td>US Hispanic</td>
<td>0%</td>
</tr>
<tr>
<td>Philippines Ivatan</td>
<td>22%</td>
<td>Italy Bergamo</td>
<td>0%</td>
</tr>
<tr>
<td>India*</td>
<td>2-6%</td>
<td>Romanian</td>
<td>0%</td>
</tr>
<tr>
<td>Japan</td>
<td>0-0.3%</td>
<td>African American</td>
<td>0.2%</td>
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<td>Korea</td>
<td>0.2%</td>
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<td></td>
</tr>
<tr>
<td>US Asians</td>
<td>4.9%</td>
<td>African</td>
<td>0-1%</td>
</tr>
</tbody>
</table>

*Carbamazepine as the leading culprit drug, data not available for Philippines Ivatan
patients to the odds in test negative patients of having CBZ-SJS/TEN is greater than 1,300, which far exceeds that of the classical example of B27 and ankylosing spondylitis (odds ratio 100-200). Although the test for HLA-B*1502 is highly informative, 3% of patients who are test positive may never develop the disease and thus may unnecessarily be denied the drug. Given the serious and life-threatening consequences of developing SJS/TEN and the availability of alternative drugs, withholding CBZ from this 3% of patients may be justifiable. These patients may be treated with other anti-epileptic medications. Fortunately other drugs (such as gabapentin, phenobarbital, lamotrigine, and valproic acid) are perhaps equally effective in controlling seizures. Taken together, the pre-prescription use of HLA-B*1502 as a test to screen out individuals at risk for SJS/TEN should be justifiable and valuable in preventing drug toxicity caused by CBZ in the high risk populations.

**Conclusion**

SJS/TEN continues to cause significant morbidity and mortality. Evidence suggests that people at risk for these serious adverse events have a genetic predisposition. Different HLA-B alleles and/or other genetic polymorphisms in the MHC region might play a major role in the pathogenesis of these immune-mediated severe cutaneous adverse drug reactions at least to carbamazepine, allopurinol, and abacavir.

Independent studies from different countries have confirmed that patients carrying the HLA-B*1502 are at high risk of SJS/TEN when exposed to CBZ. The US Food and Drug Administration and similar regulatory agencies in Canada and Taiwan have updated the CBZ drug label to include the genetic information and recommend “that patients with ancestries from areas in which HLA-B*1502 is present should be screened for HLA-B*1502 allele before starting treatment with CBZ”. Available data also suggest that HLA-B*1502 is a risk allele for SJS/TEN caused by other aromatic AEDs with a similar structure to CBZ, such as phenytoin, oxcarbazepine and perhaps lamotrigine. Such drugs should also be used with caution in individuals who test positive for HLA-B*1502.

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**References**


