Clinical Application of Pharmacogenomics: The Example of HLA-Based Drug-Induced Toxicity

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Abstract
Pharmacogenomics is gradually becoming more and more indispensable in modern medicine. In several cases, a pharmacogenomics test may alleviate serious drug-induced adverse reactions, if it precedes drug prescription. In this article, we provide an overview of the well-established HLA-based carbamazepine- and allopurinol-induced adverse reactions, as one of the most characteristic examples of the clinical application of pharmacogenomics, highlighting its regional impact in Southeast Asian populations in preventing adverse reactions of certain drug/allele pairs. This example provides useful insights towards evidence generation for policy implementation, including economic evaluation analysis, the implementation of pharmacogenomics testing procedures and monitoring of policy effectiveness, hence serving, per se or in the context of international collaborative efforts, as a model for similar cases in several national healthcare systems worldwide.

Introduction
Adverse drug reactions (ADRs) are recognized to be a significant burden on healthcare services. According to the pharmacological actions of causative drugs, ADRs are generally classified as ‘type A’ and ‘type B’ reactions, the former being dose dependent and the latter being dose independent [1]. Many severe ADRs are rare and difficult

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to predict and often discovered after a drug has been approved and used in a sufficiently large pool of patients. Severe cutaneous adverse drug reactions (SCARs) belong to type B ADRs which include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), hypersensitivity syndrome (HSS) and acute generalized exanthematous pustulosis [2]. SJS and TEN, clinically featured by different degrees of skin detachment, are the most severe types of SCARs. Based on the percentage of body surface area detached, 1–10% detachment defines SJS, 10–30% detachment defines SJS/TEN overlap, and >30% detachment defines TEN [3]. The severity of skin detachment also positively correlates with mortality, with less than 5% for SJS and as much as 50% for TEN [4]. SJS and TEN not only have skin manifestations; other organs can also be affected, causing severe complications. For instance, the ulceration of mucous membranes in the trachea, bronchi and gastrointestinal tract, hepatitis, and lymphopenia can be fatal when acute [5–9].

Most of the SJS/TEN cases are drug related. The most common causative drugs are carbamazepine (CBZ), allopurinol and phenytoin. Although the incidence of SJS/TEN is similar between Southeast (SE) Asia and Europe, the proportion of specific drug- (CBZ and phenytoin) induced SJS/TEN is much higher in SE Asia than in Europe (26 vs. 12%) [10]. Genetic variations among different populations may be an important factor for this difference.

Pharmacogenomics Study of Drug-Induced SJS/TEN: Association with HLA

HLA genes are highly polymorphic genes in the human genome. According to the IMGT/HLA database (http://www.ebi.ac.uk/ipd/imgt/hla/stats.html), more than 3,455 HLA-B alleles and 2,577 HLA-B proteins have been discovered, making HLA-B the most polymorphic gene among all the HLA genes (fig. 1).

HLA molecules can activate T cells to initiate the adaptive immune response by presenting antigen peptide to a T-cell receptor expressed on the surface of T cells. HLA class I molecules are widely expressed in almost all the karyocytes and can present the endogenous peptides to CD8+ T cells, the cytotoxic T cells. The HLA class II molecules are expressed solely in immune cells, such as dendritic cells, and present exogenous peptides to CD4+ T-helper cells. Sometimes, the cross-presentation can also occur in specific situations, such as viral infection. HLA molecules bind peptides through the peptide-binding grooves. The polymorphisms in HLA genes result in structural changes of the peptide-binding grooves; thus, the spectrum of peptides is expanded in order to ensure the successful presentation of pathogen-related proteins [11].

Genetic Studies of SJS/TEN

In the past decade, associations between drug-induced SJS/TEN and genetic factors have been studied using high-resolution HLA typing and genome-wide association study strategies. It has been found that HLA class I alleles are highly associated with drug-induced SJS/TEN in different populations. The most characteristic ones are CBZ- and allopurinol-induced SJS/TEN, in which HLA-B*1502 has been associated with SJS/TEN (table 1).

CBZ-Induced SJS/TEN

CBZ is an anticonvulsant used to treat epilepsy, bipolar disorder, and trigeminal neuralgia. Although rare, CBZ can cause life-threatening SJS/TEN in 0.23% of patients according to the historical incidence [12]. The strong association of CBZ-induced SJS/TEN with HLA-B*1502 was first identified in the Han Chinese population. In that investigation, 100% (44/44) of patients with CBZ-induced SJS/TEN were carriers of HLA-B*1502, whereas only 3% (3/101) of the CBZ-tolerant patients were HLA-B*1502 positive [13]. Their follow-up study further confirmed this association in the Han Chinese
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<th>Table 1. Association of HLA-\textsuperscript{B*}1502, A<em>3101, and B</em>5801 biomarkers with SJS/TEN</th>
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<td>Case-adapted tolerant control\textsuperscript{a}</td>
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<td><strong>HLA-B*5801/allopurinol-HSS/SJS/TEN</strong></td>
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<td><strong>HLA-B*5801/allopurinol-MPE</strong></td>
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\textsuperscript{a} The data is adapted from the study of McCormack et al. [30]. \textsuperscript{b} Although HLA-B*5801 is not significantly associated with SJS/TEN, the B*5801-DRB1*1302 haplotype is associated with allopurinol-SJS/TEN ($p = 0.00028$). cADRs = Cutaneous adverse drug reactions; NA = not available.
population [14]. Soon afterwards, several independent studies were conducted to investigate the association between \( HLA-B^*1502 \) and CBZ-induced SJS/TEN in other populations, including Thais, Malays, Indians, Africans, Caucasians, Japanese, and Koreans. However, the association only manifests in SE Asians (table 1) and not Africans, Caucasians, or East Asians (Japanese, Koreans) [15–17]. One meta-analysis combined the published case-control studies on different populations and confirmed the association in SE Asians, with an integrated OR of 79.84 (95% CI 28.45–224.06) [18]. The ethnic-specific nature of the association between CBZ-SJS/TEN and \( HLA-B^*1502 \) relates to the difference of allele frequency in different populations. The frequency of \( HLA-B^*1502 \) is higher in SE Asians than in Caucasians and Japanese (2–8 vs. <0.1%) [19]. CBZ was estimated to contribute about 35% of drug-induced SJS/TEN cases in Han Chinese [20] but only 6% of the respective cases in Caucasians [21]. The low frequency of \( HLA-B^*1502 \) and the low incidence of CBZ-induced SJS/TEN in Caucasians and Japanese may explain the inability to substantiate the association for \( HLA-B^*1502 \) in these populations.

In addition to SJS/TEN, CBZ can cause other cutaneous adverse reactions, such as maculopapular exanthema (MPE) and HSS [22]. No association of \( HLA-B^*1502 \) was found with MPE or HSS in the populations where an association of \( HLA-B^*1502 \) with SJS/TEN was observed [14, 23–27]. The meta-analysis reinforced the association between \( HLA-B^*1502 \) and CBZ-induced SJS/TEN, but not MPE or HSS in Asian populations [28]. These data suggest that the association of \( HLA-B^*1502 \) with SJS/TEN is very specific.

When the genetic study was extended to different types of CBZ-induced cutaneous ADRs (SJS/TEN, HSS, MPE), Hung et al. [14] first reported the association of \( HLA-A^*3101 \) with CBZ-induced MPE in the Han Chinese population in Taiwan (\( p = 2.2 \times 10^{-3} \), OR = 17.5). Subsequent genome-wide association studies conducted in Japanese and Europeans substantiated the association of \( HLA-A^*3101 \) with all 3 types of CBZ-induced cutaneous ADRs [28, 30]. The association of \( HLA-A^*3101 \) with HSS and SJS/TEN was also demonstrated in Koreans [31] and Canadians [32]. One meta-analysis indicated that the association of \( HLA-A^*3101 \) with CBZ-induced HSS (OR = 13.2) was stronger than with SJS/TEN (OR = 3.94) [27]. Another comprehensive meta-analysis including more studies suggested that \( HLA-A^*3101 \) was a universal risk marker, irrespective of cutaneous ADR type [SJS/TEN: \( p = 4.03 \times 10^{-6} \), OR (95% CI) = 5.65 (2.70–11.78); HSS/MPE: \( p = 4.46 \times 10^{-22} \), OR (95% CI) = 8.58 (5.55–13.28)] [33].

**Clinical Pharmacogenomics of Drug-Induced SJS/TEN: Association with HLA**

**Carbamazepine**

Given the strong association for \( HLA-B^*1502 \) with CBZ-induced SJS/TEN, the US Food and Drug Administration updated the package labeling for CBZ to highlight a high risk of SJS/TEN when patients who carry \( HLA-B^*1502 \) take CBZ and recommended that ‘patients with ancestry in at-risk populations should be screened for the presence of the \( HLA-B^*1502 \) allele prior to starting carbamazepine’ (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm). \( HLA-B^*1502 \) carriers would take alternative antiepileptic drugs, such as oxcarbazepine, phenytoin and lamotrigine. However, these alternative antiepileptic drugs share a similar structure with CBZ, and an association of \( HLA-B^*1502 \) with SJS/TEN induced by oxcarbazepine, phenytoin and lamotrigine was observed in Han Chinese and Thais [23, 24, 41]. Therefore, healthcare providers should consider avoiding phenytoin as an alternative for CBZ in patients who test positive for \( HLA-
the effectiveness of Carbamazepine Therapy was initiated in 2011 to assess Japan, a clinical trial program called Genotype-Based publications about clinical trials and cost-effectiveness produced cutaneous ADRs, especially HSS, has only recently recommended for.html). 

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It was estimated that in SE Asians, the positive predictive value and negative predictive value for HLA-B*1502 screening are 1.8% (7.7% in Han Chinese only) and 100%, respectively, and testing 461 patients would prevent 1 case of CBZ-induced SJS/TEN [28]. Several cost-effective studies have been conducted to evaluate the economics of HLA-B*1502 screening in Asian countries, including Thailand, Malaysia and Singapore. Studies in Thailand proposed the establishment of an active surveillance system to assess the prevalence of CBZ-induced SJS/TEN precisely in the Thai population before a general screening of HLA-B*1502 [42]. The study in Malaysia recommended to adopt the in-house HLA-B*1502 screening system, which is much more cost-effective than using commercial kits, to facilitate routine genotyping in the clinical setting [43]. The study in Singapore demonstrated the cost-effectiveness of HLA-B*1502 testing [44]. Therefore, the Ministry of Health in Singapore recommends HLA-B*1502 genotyping before CBZ therapy in CBZ-naive patients who have Asian ancestry, and patients from the Ministry of Health-funded restructured hospitals and institutions will get a subsidy rate of 75% of the test cost (http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2013/recommendations_for.html).

The association between HLA-A*3101 and CBZ-induced cutaneous ADRs, especially HSS, has only recently been established. So far, there have been no reports or publications about clinical trials and cost-effectiveness estimations about HLA-A*3101 genetic screening. In Japan, a clinical trial program called Genotype-Based Carbamazepine Therapy was initiated in 2011 to assess the effectiveness of HLA-A*3101 genotyping in preventing CBZ-induced SCARs in the Japanese population (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&reptno=R000008044&language=E). More investigations are required to determine whether patients should be tested for HLA-A*3101 prior to CBZ administration.

Allopurinol

Given the high prevalence and the strong association of HLA-B*5801 with allopurinol-induced SJS/TEN in Han Chinese, the Taiwan Department of Health has revised the drug labeling of allopurinol to include information of the HLA-B*5801-related risk of SJS/TEN and recommended the conduct of HLA-B*5801 testing before allopurinol treatment for the allopurinol-naive patients. The Clinical Pharmacogenetics Implementation Consortium guidelines for allopurinol dosing recommend that allopurinol should not be prescribed to patients who are positive for the HLA-B*5801 allele and state that negative testing does not exclude the possibility of developing SCARs, especially in European populations [45]. The 2012 American College of Rheumatology guidelines for the Management of Gout also highlight the high risk of allopurinol-HSS in HLA-B*5801-positive patients and recommend consideration of HLA-B*5801 testing prior to initiation of allopurinol in populations with a high HLA-B*5801 allele frequency as a risk management component [46].

Hitherto, no clinical study of HLA-B*5801 screening has been reported. A prospective clinical trial of HLA-B*5801 genotyping for the prevention of allopurinol-induced SCARs is being implemented in Taiwan; however, no results are available yet [45]. A cost-effectiveness study in Thailand suggested that HLA-B*5801 testing before allopurinol administration entails potential cost-effectiveness compared to usual care without genetic testing [47]. Other factors including ethical, legal and social implications need to be considered before HLA-B*5801 genotyping becomes generally adopted for clinical practice.

Regional Potential for the Prevention of Drug-Induced SJS/TEN for Certain Drug/Allele Pairs

As previously indicated, HLA-B*1502 is a genetic marker associated to SJS/TEN induced from CBZ, and this particular allele is common in certain populations of SE Asia. A recent review identified evidence of association in Han Chinese, Thais and Malays. No information is available from other SE Asian countries regarding the incidence of CBZ-induced SJS/TEN, based on the prevalence of HLA-B*1502 and related B75 subtypes, and the consistent association of the HLA-B*1502 allele with SJS/
TEN induced by CBZ. SE Asia is the hotbed of SJS/TEN triggered by CBZ. Since the prospective clinical trial, Taiwan succeeded in the complete prevention of SJS/TEN by establishing the $HLA-B^*1502$ pharmacogenomics test, and this strategy provides better value for money than the avoidance of CBZ enforced in several healthcare systems, including Hong Kong, Singapore and Thailand [42, 44]. Given the high prevalence of $HLA-B^*1502$ in SE Asia, implementing pharmacogenomics testing would dramatically reduce the SJS/TEN incidence triggered by CBZ in this region.

**Evidence Generation for Policy Implementation**

In Thailand and Singapore, the recommendation for providing $HLA-B^*1502$ testing for the entire population followed the health economics evidence generated by cost-effectiveness and cost-utility analyses using decision analysis models based on current practices in the respective countries. Small retrospective studies in each country in SE Asia would determine the feasibility of the adoption of this test. Evidence generation in these populations has both global and regional/national impact because descendants of SE Asian populations, such as Vietnamese and Filipinos, have migrated globally. This regional and global potential benefit led to the establishment of the Southeast Asian Pharmacogenomics research network (http://seapharm.org/), aiming to establish a biobank of patients affected with ADRs including SCAR and drug-induced liver injury. Pharmacogenomics studies will be carried out in representative samples from each nation and collaborative analysis across network members shall be carried out to increase the power of the pharmacogenomics study beyond the capacity of each individual research group. The research evidence generation within this network shall help establish novel drug/gene pairs and increase the chance of discovering of pharmacogenomics risk factors with similar diagnostic characteristics to CBZ/$HLA-B^*1502$. Within this collaborative framework, the health economics analysis can achieve more by utilizing the model generated from similar decision models and health systems across the members. Also, several Southeast Asian Pharmacogenomics Consortium members participate in other international Genomic Medicine collaborative efforts, such as the US National Institutes of Health-led Global Genomic Medicine Collaborative (G2MC) and the Genomic Medicine Alliance (http://www.genomicmedicinealliance.org) [59], hence ensuring a global representation and impact of such pharmacogenomics research.

**Implementation of Pharmacogenomics Testing Services in Clinical Settings**

The health economics studies in Thailand and Singapore provided concrete evidence for policy makers to support the use of pharmacogenomics testing for whole populations. Both health economics studies identified subgroups gaining the most benefit from the pharmacogenomics testing program. In the Thai population, patients with neuropathic pain gained more benefit than patients with epilepsy. In Singapore, Indians gained less benefit due to a lower prevalence of $HLA-B^*1502$. However, ethical considerations prohibit the provision of health services to particular ethnicities or for certain indications.

**Monitoring of the Policy Effectiveness**

Both Thailand and Singapore have reliable pharmacovigilance systems that monitored the adverse events due to healthcare products. Information from such systems is vital for the monitoring of policy effectiveness and helps convincing policy makers and the general public of the potential impact of new technology in the healthcare system. The improvement of the pharmacovigilance system for SJS/TEN in countries with this problem would provide awareness and acceptance among clinicians. The establishment of trust with direct and transparent communication is of paramount importance for the policy implementation.

**Conclusions and Future Perspectives**

In this article, we have summarized the important pharmacogenomics studies on severe cutaneous adverse events conducted in Asia and described efforts for the clinical implementation of these discoveries in the region. As the prospective clinical study conducted in Taiwan showed that preemptive genotyping can significantly reduce CBZ-induced SJS/TEN, pharmacoeconomic analysis also showed that the implementation of pharmacogenomics testing could bring significant saving for future health expenses; thus, the implementation of these tests should be carried out in these populations.

**Acknowledgements**

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