Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation

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Summary

Drug hypersensitivity reactions affect many patients leading to a variety of clinical manifestations, mainly the cutaneous adverse reactions ranging from milder skin reactions to severe cutaneous adverse reactions (SCARs). Hypersensitivity reactions are unpredictable and are thought to have an underlying genetic etiology, as suggested by case reports. With the scientific knowledge of pharmacogenomics and the evidence based on the genomic testing, it is possible to identify genetic predisposing factors for these serious adverse reactions and personalize drug therapy. The most significant genetic associations have been identified in the major histocompatibility complex (MHC) genes encoded for human leukocyte antigens (HLA) alleles. Drugs associated with hypersensitivity reactions with strong genetic predisposing factors include abacavir, nevirapine, carbamazepine, and allopurinol. In this review, strong genetic associations of drug-induced SCARs are highlighted so as to improve drug safety and help to select optimal drugs for individual patients. Further investigation, however, is essential for the characterization of other genes involved in the hypersensitivity reactions with the use of several genetic strategies and technologies. (Asian Pac J Allergy Immunol 2014;32:111-23)

Keywords: pharmacogenomics, hypersensitivity, abacavir, nevirapine, carbamazepine, allopurinol, Stevens-Johnson syndrome, toxic epidermal necrolysis

Introduction

Adverse drug reactions (ADRs) are common in clinical practice occurring in up to 6-10% of patients and remain an important public health problem as they are potentially life-threatening.1, 2 An ADR has been defined as a noxious or unintended response to a drug that is administered in standard, normal doses by the proper route for the purpose of prevention, diagnosis, or treatment of a specific disease.3 ADRs are pharmacologically classified into two basic types: type A and type B. Type A ADRs are due to pharmacological actions of the drug which are dose dependent and thus predictable. Type B ADRs are hypersensitivity reactions which are less dependent on dose, unpredictable, based on the pharmacological effects of the causative drug, and primarily determined by host genetics.4 In the clinical setting, the common ADRs are type A reactions which include toxic effects, side effects, secondary effects and also drug interactions. Type B reactions have been noted in a minority of cases and comprise approximately 10-15% of all ADRs, including hypersensitivity drug reactions. About 5%–10% of type B ADRs are immune-mediated hypersensitivity reactions with the involvement of IgE- or T-lymphocytes, and to a lesser extent involving an immune complex or cytotoxic reactions. All other hypersensitivity drug reactions without an immune mechanism are classified as non-immune (non-allergic) hypersensitivity reactions.12 The Gell and Coombs classification divides drug hypersensitivity and other immune reactions into four categories, known as type I-IV reactions.5 Type I hypersensitivity reactions (immediate-type reactions) are caused by the formation of
drug/antigen-specific IgE and mainly cause pruritus, angioedema, urticaria, anaphylaxis and bronchoconstriction. Type II hypersensitivity reactions, or so-called cytotoxic reactions, are based on IgG or IgM-mediated cytotoxic mechanisms, accounting primarily for blood cell dyscrasias, such as hemolytic anemia and thrombocytopenia. Type III hypersensitivity reactions are mediated by intravascular immune complexes. Type IV reactions are known as delayed hypersensitivity reactions (DHR), which are T cell mediated. Based on the T-lymphocyte subset and cytokine expression, type IV hypersensitivity reactions can be classified into four subtypes (type IVa-IVd) (Figure 1).

Hypersensitivity drug reactions (HDRs): The type B adverse drug reactions (ADR-B)

Hypersensitivity drug reactions (HDRs) are type B reactions and may result in severe consequences which are potentially life-threatening and lethal. Drug hypersensitivity is an important clinical problem, defined as an objective reproducible symptom started by exposure to a defined drug at a dose tolerated by normal people and thought to be immunologically mediated. Hypersensitivity reactions consist of cutaneous adverse drug reactions (e.g., urticarial, exanthema, and angioedema), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS) or drug induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS). These cutaneous ADRs are collectively classified as severe cutaneous adverse reactions (SCARs). Single-organ or multiple-organ involvement such as drug-induced liver injury (DILI) and pulmonary disorders which are non-immunologically mediated can also occur. Any drug can elicit hypersensitivity reactions. Antiretrovirals, allopurinol, antiepileptics, non-steroid anti-inflammatory drugs (NSAIDs), and several antibiotics are the drugs mostly causing HDRs.

Human leukocyte antigens (HLA)-associated delayed drug-induced hypersensitivity reactions

Delayed-type hypersensitivity reactions (or type IV reactions) are T-cell mediated, occurring at least after 3 days of exposure to the antigen or drugs. There are various factors that come into play

Figure 1. Classification of adverse drug reactions
contributing to patients’ susceptibility to drug hypersensitivity (Figure 2). On initial exposure of the drug, T cells are primed and on repeated exposure the memory pool is re-stimulated. The key proteins that mediate T-cell immune responses are the human leukocyte antigen (HLA) molecules encoded within the major histocompatibility complex (MHC) gene family. HLA molecules have a direct role in the pathogenesis of drug hypersensitivity because they are the primary elements in T cell stimulation. Among the genetic factors involved in the development of drug hypersensitivity, HLA alleles play an important role. MHC spans approximately 3.6 Mb on band 6p21.3 of the short arm of chromosome 6. MHC consists of ‘classical’ class I (HLA-A, HLA-B, and HLA-C), class II (HLA-DR, HLA-DP, and HLA-DQ), and class III genes. Theoretically, class I and class II molecules present peptides to CD8+ and CD4+ T cells, respectively. The MHC is extremely polymorphic and there are several acute drug reactions associated with specific HLA alleles. Significant ones include hypersensitivity to abacavir and HLA-B*57:01/abacavir-induced hypersensitivity and HLA-B*15:02/SJS-induced by carbamazepine in Han Chinese. There are numerous other HLA alleles implicated in drug-induced SCARs.

Several genetic studies have been performed to discover the genetic predisposition to drug hypersensitivity and gain insight into phenotypic diversity. There is considerable interest in the potential implication of genetic variations in association studies for HDRs. The genotype-phenotype correlation is still lacking due to low incidence, difficulty of patient enrollment, and small sample size. With the genetic research findings, HDRs which are currently unpredictable could be both predictable and preventable in the future as we develop a better definition of drug response phenotypes. The purpose of this review is to summarize the most significant findings to date of drug-induced hypersensitivity syndromes in various populations (Table 1).

Model and concept for hypersensitivity drug reactions (HDRs)

Three models have currently been proposed to explain the MHC-dependent T-cell stimulation by distinct drugs, leading to an immune response.

a) The hapten/prohapten model

This model proposes that a small and immunologically neutral molecule becomes immunogenic after binding with a protein. Usually a

![Figure 2. Systems involved in drug hypersensitivity. Adapted from Pichler et al.](image)
drug that is not antigenic due to its small size will bind with a high molecular weight protein, becomes antigenic and stimulate an immune response. Pro-hapten molecules become antigenic through metabolism to reactive intermediates which then bind covalently or haptenate with proteins. They are then presented via the HLA molecules to antigen receptors at the first encounter without a sensitization phase. A drug exclusively stimulates T cells directly without forming a hapten, in an HLA-dependent manner. This model involves a chemically inert drug which is unable to form a covalent bond with larger proteins and interacts directly with T cell receptors (TCR) or MHC molecules. This pathway is metabolism or processing independent, due to the direct interaction of the drug with the TCR or MHC molecules.

**Table 1. Studies of HLA and drug hypersensitivity**

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Syndrome</th>
<th>Alleles</th>
<th>Ethnic</th>
<th>Odd ratios (95% CI)</th>
<th>P-value</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HSS/DIHS/DRESS (rash, fever, gastrointestinal, respiratory symptoms)</td>
<td>HLA-B*57:01</td>
<td>White</td>
<td>1945 (110-34,352)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Black</td>
<td>900 (38-21,045)</td>
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<td></td>
<td></td>
<td>Australian</td>
<td>117 (29-481)</td>
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<tr>
<td>Allopurinol</td>
<td>SJS/TEN</td>
<td>HLA-B*58:01</td>
<td>Han Chinese</td>
<td>580.3 (34.4-9780.9)</td>
<td>4.7*10-41</td>
<td>41</td>
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<td></td>
<td></td>
<td></td>
<td>Thai</td>
<td>348.3 (19.2-6336.9)</td>
<td>1.6*10-13</td>
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<td></td>
<td></td>
<td></td>
<td>Korean</td>
<td>179.24 (10.19-3151.74)</td>
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<tr>
<td>Carbamazepine</td>
<td>HSS/DIHS/DRESS</td>
<td>HLA-B*15:02</td>
<td>Han Chinese</td>
<td>38.6</td>
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<td></td>
<td></td>
<td>HLA-B*15:02</td>
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<td>38.6 (2.68-2239.5)</td>
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<td>HLA-B*15:02</td>
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<td>1357 (193.4-8838.3)</td>
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<td>HLA-B*15:11</td>
<td>Korean</td>
<td>18 (2.3-141.2)</td>
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<td>HLA-B*15:11</td>
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<td>HLA-A*31:01</td>
<td>Northern European</td>
<td>25.93 (4.93-116.18)</td>
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<tr>
<td>Nevirapine</td>
<td>HSS/DIHS/DRESS (fever, hepatitis, skin rash)</td>
<td>HLA-A*31:01</td>
<td>Japanese</td>
<td>10.8 (5.9-19.6)</td>
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<td>European</td>
<td>26.4</td>
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<td>Delayed rash (MPE)</td>
<td>HLA-A*31:01</td>
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<td>8.6</td>
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<td>Canadian</td>
<td>8.6 (1.67-57.50)</td>
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**b) The p-i model**

The hapten-independent or p-i model proposed that the parent drug can elicit a specific immune response by directly interacting with immune receptors at the first encounter without a sensitization phase. A drug exclusively stimulates T cells directly without forming a hapten, in an HLA-dependent manner. This model involves a chemically inert drug which is unable to form a covalent bond with larger proteins and interacts directly with T cell receptors (TCR) or MHC molecules. This pathway is metabolism or processing independent, due to the direct interaction of the drug with the TCR or MHC molecules.

**c) The altered repertoire model**

This concept proposes that drugs can alter the repertoire of self-peptides presented to T-cells by occupying a specific site within the antigen-binding cleft of the HLA molecule, and thus leading to the
immune response. Evidence suggests that unmodified abacavir binds non-covalently to the floor of the peptide binding groove of \textit{HLA-B*57:01} with exquisite specificity, changing the shape and chemistry of the antigen-binding cleft of the HLA molecule, thereby altering the repertoire of peptides bound to \textit{HLA-B*57:01}. Hypersensitivity responses are triggered by activation of abacavir-specific T-cells caused by the resultant peptide-centric ‘altered self’. There have been suggestions about the possibility that the altered repertoire mechanism is involved in abacavir-induced hypersensitivity and carbamazepine-induced SJS/TEN.

**Severe cutaneous adverse reactions (SCARs)**

1. **Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (SJS/TEN)**

SJS and TEN are a part of a single disease spectrum which is life threatening. The clinical features of SJS/TEN include mucous membrane erosions, target lesions, and epidermal necrosis with detachment (Figures 3A and 3B). SJS occurs when epidermal detachment occurs over less than 10% of the total body surface area (BSA), whereas TEN is defined as epidermal detachment of more than 30% of the BSA and SJS/TEN overlap is detachment of 10-30% of BSA. The most severely affected parts are the mucous membrane of mouth, eyes, and vagina. When the rash appears, it is warm and red. The dermal layer gets filled with fluid and blisters are formed. The skin then begins to peel off. Most of the cases of SJS/TEN are due to the adverse cutaneous effects of drugs (80-95%). Commonly implicated drugs in SJS/TEN are sulfa-antimicrobials, allopurinol, aromatic amine anticonvulsants, antiretrovirals, and NSAIDs. SJS/TEN have a high potential for severe morbidity and mortality with TEN having the higher mortality (30-35%).

![Figure 3](image_url) **Figure 3.** The characteristic features of severe cutaneous adverse drug reactions with (A) Stevens-Johnson syndrome (SJS), (B) toxic epidermal necrolysis (TEN), (C) drug reaction with eosinophilia and systemic symptoms (DRESS), and (D) acute generalized exanthematous pustulosis (AGEP).
2. Drug reactions with eosinophilia and systemic symptoms (DRESS)/ drug induced hypersensitivity syndrome (DIHS)/hypersensitivity syndrome (HSS) (DRESS/DIHS/HSS)

DRESS syndrome is another rare, potentially life-threatening clinical condition characterized by dermatologic manifestations and involvement of internal organs (Figure 3C). The immunopathogenesis of DRESS remains elusive and not well understood. Numerous Drugs are considered to be the main agents inducing symptoms of DRESS, including phenytoin, allopurinol, antiretrovirals, and NSAIDs. Erythematous morbiliform rash is the commonly encountered cutaneous finding. Systemic abnormalities are related with hematologic, gastrointestinal, hepatic, renal, cardiac, neurologic, and endocrine symptoms. The sequences for DRESS are the prodromal symptoms of pruritus and fever followed by skin rash, then lymphadenopathy, pharyngitis and finally systemic involvement. A fairly diffuse facial edema can appear in patients with DRESS which can be mistaken for angioedema.

3. Acute generalized exanthematous pustulosis (AGEP)

AGEP is another rare type of drug eruption which begins with erythema or edema in the intertriginous areas or face. Then, rapidly progressive fine non-follicular sterile pustules are formed (Figure 3D). The onset of symptoms is quick after administration of the drug which is the striking characteristic of AGEP. Other notable symptoms present are fever, neutrophilia, and eosinophilia. The drugs causing AGEP are aminopenicillins, carbamazepine, macrolides, quinolones, diltiazem, and antimalarials. The main pathogenesis is a delayed type of hypersensitivity related to CD4+ T cells which express IL-8 and leads to subsequent infiltration by neutrophils and causes pustule formation.

Pharmacogenetics of Drug Hypersensitivity

1. Abacavir

Abacavir is a guanosine nucleoside reverse transcriptase inhibitor (NRTI) which is utilized as a component in combined antiretroviral therapy (cART) used to treat human immunodeficiency virus type I (HIV-1) infection. Abacavir competitively inhibits the viral reverse transcriptase enzyme, suppressing HIV’s ability to convert its RNA genome into DNA before insertion into host cell’s genome. The main adverse event associated with Abacavir treatment is a potentially life-threatening hypersensitivity reaction, commonly referred to as abacavir-hypersensitivity reaction (ABC-HSR). About 1-9% of patients exposed to abacavir may develop an HSR during the first 6 weeks of treatment. ABC-HSR is clinically manifested by a rash, fever, gastrointestinal, constitutional, and respiratory symptoms. Upon the discontinuation of abacavir, the symptoms disappear. Although the immunological basis of ABC-HSR is not completely understood, the HLA-B*57:01 allele has an association with HSR in a study by Mallal and colleagues. The results suggested that HLA-B*57:01 was present in 78% of the patients with abacavir hypersensitivity, but only 2% of the abacavir tolerant patients carried the allele. As reported by Hetherington et al., HLA-B*57 was present in 39 (46%) of 84 patients versus four (4%) of 113 controls (p <0.0001) in a retrospective, case-control study. Results suggest that the pharmacogenetic results could be used to prevent the adverse reactions of pharmaceuticals. ABC-HSR has shown racial background as a risk factor, with white patients generally having a higher risk than black patients.

In addition, it has been reported that abacavir-specific T cell responses can be activated only in response to the abacavir-treated antigen presenting cells (APCs) possessing the HLA-B*57:01 molecule, but not in response to APCs expressing the closely related allotypes HLA-B*57:03 (Asp114Asn; Ser116Tyr), HLA-B*57:02 (Asp114Asn; Ser116Tyr; Leu156Arg) and HLA-B*57:08 (Met45Thr; Ala46Glu; Val97Arg; Val103Leu). The mechanism involved in restricted generation of immunogenic complexes in ABC-HSR involves both the hapten/prohapten model and anchor site modification/occupation model. Abacavir, or a metabolite, modifies a restricted set of cellular proteins. The modified protein undergoes proteasome-mediated degradation to produce peptide fragments, including a drug-haptenated peptide, which are then loaded onto HLA-B*57:01 and stimulate antigen-specific CD8+ T cells. The anchor site modification/occupation model is explained by the attachment of abacavir, or a metabolite, to the F-pocket of HLA-B*57:01 molecule, leading to a change in the peptide repertoire that is capable of binding and elicits an immunogenic reaction.

The frequency of HLA-B*57:01 varies in different ethnic populations, such as <1% in sub-
Saharan Africans, 1% to 2% in Mediterraneans, 5% to 20% in Indians, 0% in Chinese and 4% to 10% in Thais. Due to the low frequency of the HLA-B*57:01 allele, ABC-HSR was less frequent in Taiwanese HIV-infected patients.33 Interestingly, the issue of whether HLA-B*57:01 screening to prevent the hypersensitivity reaction to abacavir studied by Mallal et al. showed that HLA-B*57:01 screening reduced the risk of hypersensitivity reaction to abacavir in the Prospective, Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) study. The incidence of confirmed abacavir hypersensitivity was 2.7% in the control group versus 0% in the HLA-B*57:01 screened group (p < 0.001).34 Similarly in a prospective Western Australian HIV cohort study, involving 260 abacavir-naïve patients, there were no cases of abacavir hypersensitivity among 148 HLA-B*57:01 non-carriers.35 This evidence provides a translational roadmap from discovery of genetic associations through to implementation of pharmacogenetic screening in routine clinical settings. Abacavir should not be used in patients who test positive for HLA-B*57:01. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines suggest the HLA-B*57:01 screening in abacavir-naïve patients prior to initiation of abacavir therapy is consistent with the recommendations of the FDA, the US Department of Health and Human Services, and the European Medicines Agency.28

1. Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is the most common urate-lowering agent used for the treatment of gout.36,37 The reported side effects of allopurinol include skin rashes and hypersensitivity reactions manifesting as vasculitis, hepatitis, epidermal necrosis, nephritis, and fever.38 In a case report by Engel et al., a woman admitted to hospital after taking allopurinol had the symptoms of DRESS and symptoms were resolved after allopurinol was withdrawn.39 Allopurinol has been highly associated with SJS/TEN based on data from the RegisSCAR/ EuroSCAR registry.40

The HLA-B*58:01 allele has been proposed as the genetic marker of allopurinol-induced SCARs. The HLA-B*58:01 allele has been associated with allopurinol-induced SCARs in Han Chinese patients living in Taiwan where almost all patients developing SCARs carry this allele.41 In the Thai population, 100% of the allopurinol-induced SJS/TEN patients carried HLA-B*58:01.42 Also, HLA-B*58:01 was significantly associated with higher risk of SCARs in the Thai (OR:108.33, P <0.01)43 and Korean populations (OR:179.24).44 A study in Portuguese patients showed the high frequency of HLA-B*58:01, with an OR similar to European patients with SJS/TEN.45 A meta-analysis conducted by Somkrua et al. found significant associations between the HLA-B*58:01 allele and allopurinol-SJS/TEN in both Asian and non-Asian populations.46 A genome-wide association study (GWAS) in Japanese patients detected a strong association of HLA-B*58:01 with allopurinol-SJS/TEN.47 Given the strong association between HLA-B*58:01 and allopurinol-SCARs, screening of patients is warranted to prevent serious adverse reactions. Recently, a guideline has been released by CPIC for the use of allopurinol when HLA-B*58:01 genotyping results are available.48 In addition, the American College of Rheumatology guidelines for the management of gout has been updated in 2012 and one of the significance and innovations of these guidelines is HLA-B*58:01 screening in subpopulations where both the HLA-B*5801 allele frequency is elevated and HLA-B*5801–positive subjects have a very high risk for allopurinol-induced SCARs, such as those of Han Chinese and Thai descent, as well as Koreans with stage 3 or worse of chronic kidney disease. A recent economic evaluation study by Saokaew et al. demonstrated the cost-effectiveness of HLA-B*58:01 screening prior to allopurinol therapy in preventing allopurinol-induced SJS/TEN in the Thai population.49

2. Carbamazepine

Carbamazepine, a commonly prescribed drug, is used to treat epilepsy, trigeminal neuralgia, bipolar disorder, and chronic pain. Carbamazepine, however, is associated with serious adverse events like SJS/TEN.50,51 Although inconclusive, carbamazepine elicits an immunogenic response by T cell stimulation following the p-i model concept because carbamazepine has been reported to reactivate CD4+ and CD8+ T-cells in the absence of antigen processing.17 The HLA-B*15:02 allele is highly associated with carbamazepine-induced SJS/TEN in Han Chinese, but not in Caucasian and Japanese populations. The CPIC and US FDA has recommended genetic screening for patients of Asian ancestry before starting carbamazepine therapy for the HLA-B*15:02 allele and carbamazepine should not be used in patients who have at least once copy of the between HLA-B*15:02 allele.52,53

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B*15:02 and carbamazepine-induced SJS/TEN has been reported in several studies in Han Chinese populations.\(^{50,54}\) In the study conducted by Zhang and colleagues, the HLA-B*15:02 allele was present in 94.1% (16/17) of carbamazepine-induced SJS/TEN patients as compared to only 9.5% (2/21) of carbamazepine tolerant patients in the mainland Han Chinese population.\(^{55}\) Similarly, the results of studies conducted in Malaysia, India, Singapore, and Thailand support this strong association.\(^{56-61}\) HLA-B*15:02 screening prior to initiation of carbamazepine therapy in subjects recruited throughout Taiwan, and withholding carbamazepine in HLA-B*15:02-positive patients reduced the incidence of SJS/TEN. None of the patients developed SJS/TEN which was significantly different from the estimated historical incidence of 0.23%.\(^{62}\)

The frequency of HLA-B*15:02 varies markedly among different populations suggesting that different alleles may also function in carbamazepine-induced SJS/TEN. The HLA-A*31:01 allele is proposed as a marker for the hypersensitivity syndrome in European (\(P=3.5\times10^{-8}\))\(^{63}\) and Japanese (OR:10.8, \(P=3.64\times10^{-15}\))\(^{64}\) populations. Recently, Amstutz et al. investigated HLA-A*31:01 and HLA-B*15:02 in pediatric patients from North America with various ancestry and found that HLA-A*31:01 was a significant predictor of carbamazepine-induced HSS (OR=26.4, \(P=0.0025\)) and maculopapular exanthema (MPE) (OR=8.6, \(P=0.0037\)), but not with carbamazepine-induced SJS. HLA-B*15:02, which was, however, associated with carbamazepine-SJS (OR=38.6, \(P=0.002\)), but not HSS or MPE, which indicates the phenotypic specificity of HLA genes.\(^{65}\) Previously, HLA-A*31:01 was associated with carbamazepine-induced MPE/HSS in Han Chinese or Chinese descendants.\(^{66}\) A recent HLA genotype-phenotype correlation in carbamazepine-induced hypersensitivity reaction analysis in Han Chinese also reiterated the strongest association of HLA-B*15:02 with carbamazepine-induced SJS/TEN and HLA-A*31:01 linked to carbamazepine-induced MPE/DRESS. The HLA-B*15:02 allele, however, had no association with carbamazepine-induced MPE/DRESS.\(^{15}\) HLA-B*15:11 has been associated with carbamazepine-induced SJS/TEN in Japanese and Korean patients.\(^{67,68}\) HLA-B*15:02 and HLA-B*15:11 belong to the same HLA-B75 family. Interestingly, other members of the HLA-B75 serotype, including, HLA-B*15:08 and HLA-B*15:21 have been reported to be associated with the carbamazepine-induced SJS/TEN in various populations.\(^{56,61}\) This is possibly explained by the ability of the members of HLA-B75 to present carbamazepine to activate carbamazepine-specific cytotoxic T lymphocytes (CTLs).\(^{69}\)

It has been observed that there is a high frequency of clinical cross-reactivity among aromatic amine anticonvulsants such as carbamazepine, phenytoin, oxcarbazepine, and lamotrigine.\(^{70}\) A highly significant mutual risk for cross reactivity of rashes with these anticonvulsants (\(P<0.001\)) was observed in Chinese populations.\(^{71}\) There are reports of a similar genetic predisposition to SJS/TEN among the users of aromatic amine anticonvulsants. HLA-B*15:02 which was found to be strongly associated with phenytoin-induced SJS in the Thai population.\(^{58}\) Similarly, in a case-controlled study carried out by Hung et al., HLA-B*15:02 was associated with SJS induced by phenytoin, oxcarbazepine, and lamotrigine in the Han Chinese population, suggesting the avoidance of these drugs in the carriers of the culprit allele can be considered to be a good choice.\(^{72}\) This spectrum of HLA-B*15:02 in inducing SJS among the anticonvulsant users is due to the possession of a similar aromatic ring in their chemical structure.

The HLA-B*15:02 allele is found in high prevalence among the people in East and South-east Asian countries. The potentially lethal nature of SJS/TEN makes the treatment more costly causing a burden to the society. It is necessary to prevent carbamazepine-induced SJS/TEN and it is also important to consider the cost of genotyping in clinical practice. Locharennkul et al. demonstrated the lower cost of screening for HLA-B*15:02 (27 SUS or 1,000 Baht per test) was lower than SJS treatment costs when preventing carbamazepine-induced SJS among Thai patients.\(^{73}\) Recently, Tiamkao et al. compared the treatment cost for carbamazepine-induced SJS/TEN and the cost of HLA-B*15:02 screening in the Thai population. The HLA-B*15:02 screening before initiating carbamazepine was found to be cost effective, with a saving of 98,549.94 baht per 100 cases of carbamazepine-prescribed patients.\(^{74}\) Consequently, the National Health Security Office (NHSO), Thailand is currently implementing a pilot project of HLA-B*15:02 screening for the Thai population to eradicate the carbamazepine and oxcarbazepine-induced SJS/TEN in the Bangkok area where
carbamazepine and oxcarbazepine are prescribed for many indications.

3. Nevirapine

Nevirapine, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI), is used for the treatment of HIV-1 infection, but it frequently causes HSRs characterized by various combinations of fever, hepatitis, and skin rashes.\(^5,9,75,76\) The development of the hypersensitivity syndrome in patients using nevirapine was first reported by Bourezane et al. in 1998 when a man treated with stavudine, indinavir, and nevirapine developed a painful palmoplantar erythema on day 15. After the complications of maculopapular rash enlarged lymph nodes and hepatosplenomegaly on day 24, all medications were stopped on day 34. He was then treated with IV methylprednisolone for 3 days and all the manifestations resolved within 10 days. On day 60 he was rechallenged with stavudine and indinavir, without any complications.\(^77\)

Genetic predisposition to nevirapine-induced HSR (NVP-HSR) has been reported in class I and class II HLA alleles across different populations. The HLA-Cw\(^*04\) allele was observed in 20.51% of Thai HIV patients with nevirapine-induced rash as compared with only 7.50% of nevirapine-tolerant Thai HIV patients (P=0.009)\(^78\) and Han Chinese (OR:3.611, \(P = 0.03\)).\(^79\) Significantly, a case-controlled association study in Thai HIV patients revealed an association with nevirapine-induced skin rash. The HLA-B\(^*35:05\) allele occurred in 17.5% of patients with nevirapine rash compared with only 1.1% observed in nevirapine tolerant patients [odds ratio (OR)=18.96; \(P\) corrected for multiple comparison, \(P_c=4.6\times10^{-5}\)] and 0.7% in the general Thai population (OR=29.87; \(P_c=2.6\times10^{-5}\)).\(^80\) In a study showing the genetic variability in metabolizing enzymes, Ciccacci and colleagues (2013) reported cases that developed SJS/TEN among HIV patients treated with nevirapine-based regimens in Mozambique. Individuals with CYP2B6 G516T and T983C single nucleotide polymorphisms (SNPs) were found to be associated with SJS/TEN. Patients with the G516T variant allele had about a twofold higher risk of developing SJS/TEN (OR=1.8). In CYP2B6 T983C SNP, the C allele was significantly associated with a higher risk of developing SJS/TEN (OR=4.2, \(P=0.0047\)).\(^81\) A recent study by Yuan et al. supports these findings in a case-controlled 11 country design study. They found strong associations of cutaneous adverse events with CYP2B6 G516T (OR=1.66) and HLA-Cw\(^*04\) (OR=2.51) in all the populations studied. Importantly, Asians, particularly Thais, showed cutaneous adverse reactions associated with HLA-B\(^*35\) (OR=3.47 for Asians; 5.65 for Thais).\(^82\)

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At the present time, HLA-B genotyping is considered the standard of care in clinical practice before starting therapy with the above mentioned drugs. HLA-B genotyping is available in clinical practice, providing appropriate clinical monitoring and patient counseling about phenotype findings and recommendations about therapy. Currently, “pharmacogenetic tests” and “pharmacogenomic card” have been successfully implemented in clinical practice in Thailand at the Laboratory for Pharmacogenomics, Somdech Phra Debaratana Medical Center, Ramathibodi Hospital. The results of the pharmacogenetic tests are provided along with the interpretation associated with HLA-B alleles and SCARs for a particular drug. The information required for the clinician and the patient is provided. Also, the patients are screened for the alleles present which are associated with the ADRs related to the use of the drugs concerned. Patients and clinicians are informed about the presence of such alleles on the pharmacogenomic card which will aid in preventing drug induced ADRs in case the patient uses the drug in the future (Figure 4A-4D).

The interpretation of clinical HLA-B genotyping tests provides useful information with regard to abacavir, allopurinol, and carbamazepine treatment. The HLA-B alleles statuses do not affect pharmacokinetics and pharmacodynamics of the aforementioned drugs. The specific-drug/ pharmacogenetic marker (specific-HLA-B marker) results are presented as either “positive” or “negative” for the particular HLA-B allele, with no intermediate phenotype. The absence of HLA-B\(^*57:01\) alleles, reported as “negative” on a specific-HLA-B genotype test, have a very low risk of abacavir hypersensitivity reactions, whereas for the individuals who are HLA-B\(^*57:01\)-positive with the presence of at least one HLA-B\(^*57:01\) allele, abacavir is not recommended because of the high risk of abacavir-induced hypersensitivity. Both the heterozygote and homozygous variants are reported as “positive” on a specific-HLA-B genotyping test. Similar guidelines for the pharmacogenetic test for
allopurinol are recommended, with \( \text{HLA-B*58:01} \)-positive individuals contraindicated for taking allopurinol, due to the significantly increased risk of allopurinol-induced SCAR. Genotyping results are presented as “positive” with the presence of one or two copies of \( \text{HLA-B*15:02} \), and “negative” if no copies of \( \text{HLA-B*15:02} \) are present in the

**Conclusion**

This review has presented evidence of the genetic associations of drug hypersensitivity reactions with reference to commonly used drugs.
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like abacavir, nevirapine, carbamazepine and allopurinol in different indications. The highly positive predictive value of HLA-B*57:01 in abacavir-induced cutaneous adverse reactions demands implementation of pharmacogenetic screening in routine clinical settings. Abacavir should not be used in patients who test positive for HLA-B*57:01. Similarly, a screening test to detect the presence of an HLA-B*58:01 allele could be useful to prevent allopurinol-SCARs. The US FDA recommendation for genetic screening of HLA-B*15:02 before prescribing carbamazepine might be useful only for the patients of Asian ancestry. Ethnicity has an important role in inducing the adverse events by the alleles in question.

Although rare, SCARs have a high morbidity and mortality rate. This discovery of potential implicated genes will help develop preventative strategies and make the medication safer. From these impressive findings, it is just a matter of time before these results can be used in clinical practice to prevent the specific toxic effects of a drug. Several issues like equity in health, ethical principles, and legal challenges need to be considered in clinical practice. There are several factors related to the patient and drugs which have effects on the frequency and severity of drug hypersensitivity. It has to be noted, however, that without the exposure of an individual to the drug, there will be no adverse effects even if an individual carries the risk gene (Figure 5). Since most drug hypersensitivity reactions are rare, it is imperative that a multicenter, multinational collaboration is created to collect enough case and control samples across various ethnic populations to ensure sufficient statistical power for the detection of genetic biomarkers, both in exploratory and validation studies. To successfully translate the discovery into clinical practice, the accurate phenotypic characterization of patients is essential and, crucial. From a drug-safety standpoint, the negative-predictive values of the pharmacogenetic tests should be approximately 100%. The laboratory tests should be cost-effective, widely available and easy to implement.

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**Figure 5.** Strong genetic associations of drug-induced SCARs are highlighted. It has to be noted that without the exposure of an individual to the drug, there will be no adverse effects even if an individual carries the risk gene.
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Conflicts of interest
The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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