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 antigen*s (*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)***

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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 a 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.[1,2] 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

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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).[5]

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.[6,7] Clinical manifestations of drug hypersensitivity 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-organs involvement such as drug-induced liver injury (DILI) and pulmonary disorders which are non-immunologically mediated can also occur.[8] Any drug can elicit hypersensitivity reactions. Antiretrovirals, allopurinol, antiepileptics, non-steroid anti-inflammatory drugs (NSAIDs), and several antibiotics are the drugs mostly causing HDRs.[9,10]

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 into play

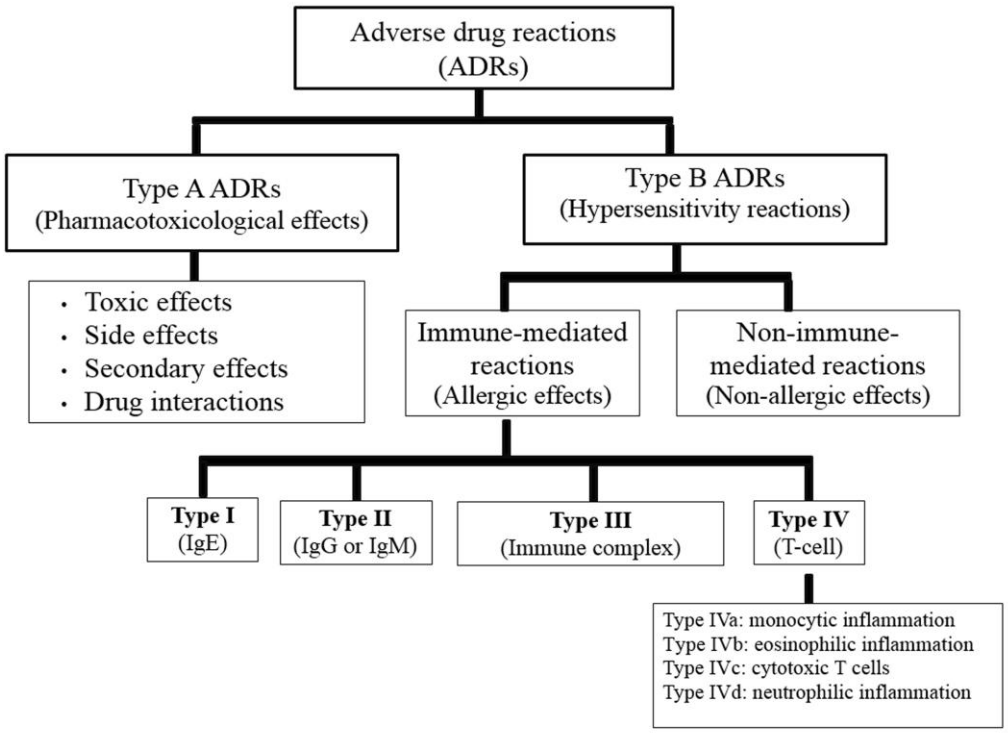

Figure 1. Classification of adverse drug reactions

contributing to patients' susceptibility to drug hypersensitivity (Figure 2).[11] 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.[12] 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.[13] 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.[14] 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.[15] 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

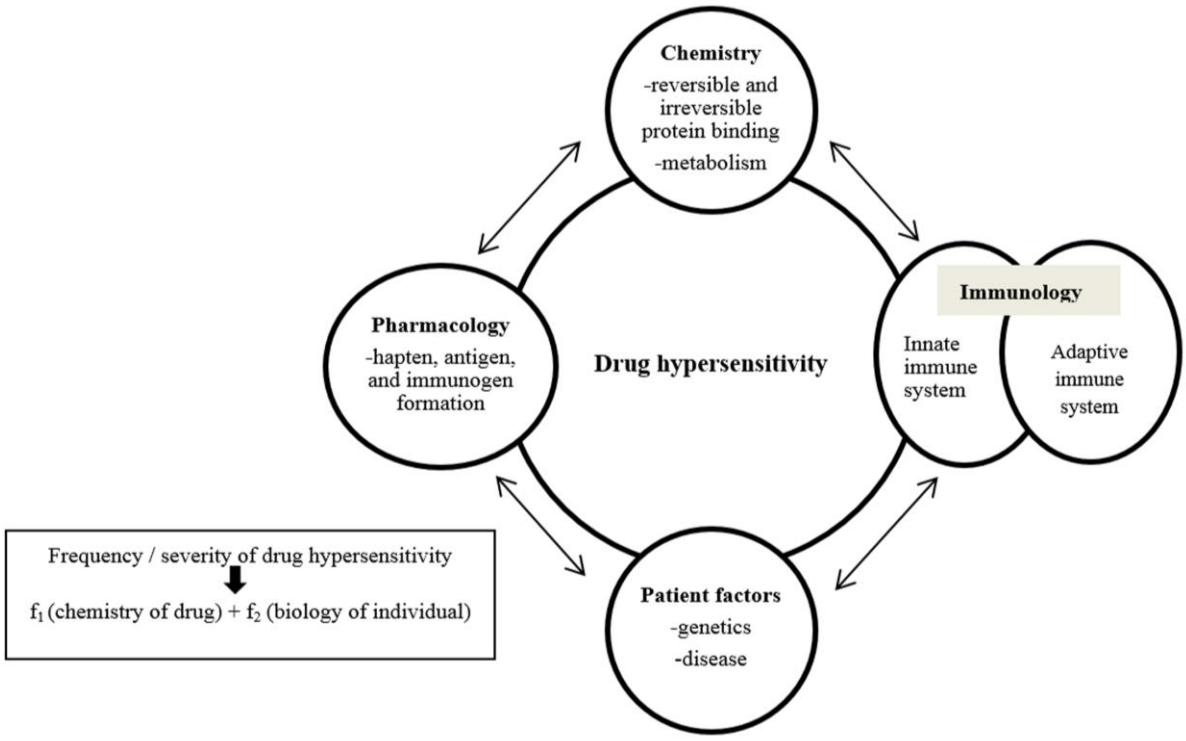

Figure 2. Systems involved in drug hypersensitivity. Adapted from Pichler et al.[8,11]

Table 1. Studies of HLA and drug hypersensitivity

Therapeutic Agents	Syndrome	Alleles	Ethic	Odd ratios (95% CI)	P-value	Ref
Abacavir	HSS/DIHS/DRESS (rash, fever, gastrointestinal,respiratory symptoms)	HLA-B*57:01	White	1945 (110-34,352)	<0.0001	32
			Black	900 (38-21,045)		32
			Australian	117 (29-481)		30
Allopurinol	SJS/TEN	HLA-B*58:01	Han Chinese	580.3 (34.4-9780.9)	4.7*10-24	41
			Thai	348.3 (19.2-6336.9)	1.6*10-13	42
			Korean	179.24 (10.19-3151.74)		44
Carbamazepine	SJS/TEN	HLA-B*15:02	Han Chinese	38.6		65
		HLA-B*15:02	Canadian	38.6 (2.68-2239.5)	0.002	65
		HLA-B*15:02	Han Chinese	1357 (193.4-8838.3)	1.6*10-41	66
		HLA-B*15:11	Korean	18 (2.3-141.2)	0.011	67
		HLA-B*15:11	Japanese	9.76 (2.01-47.5)	0.0263	68
		HLA-A*31:01	Northern European	25.93 (4.93-116.18)	8*10-5	63
		HLA-A*31:01	Japanese	10.8 (5.9-19.6)	3.64*10-15	64
	HSS/DIHS/DRESS	HLA-A*31:01	European	26.4	0.0025	65
			Canadian	26.4 (2.53-307.89)		65
	Delayed rash (MPE)	HLA-A*31:01	Northern European	12.41 (1.27-121.03)		63
			European	8.6	0.0037	65
			Canadian	8.6 (1.67-57.50)		65
			Northern European	8.33 (3.59-19.36)		63
Nevirapine	HSS/DIHS/DRESS (fever, hepatitis, skin rash)	HLA-B*35:05	Thai	18.96 (4.87-73.44)	4.6*10	80
		HLA-Cw*04	Han Chinese	3.611 (1.135-11.489)	0.03	79
			Thai			78
			Asians, White, Black	2.51 (1.73-3.62)	6.7*10-7	82
		CYP2B6 G516T	Mozambique	1.8		81
			Asians	3.47		82
			Asians, White, Black	1.66(1.29-2.15)	5.5*10-5	82
		CYP2B6 T983C	Mozambique	4.2	0.0047	81

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-specific T cells and form an immunological synapse.[5,16] Re-exposure of sensitized individuals will result in proliferation of memory T cells, after which an inflammatory response will appear within 24-72 h. Known examples of T cell responses induced by this concept include responses to penicilloyl peptides in the presence of penicillins, and responses to nitrososulfamethoxazole-modified peptides formed during sulfamethoxazole treatment.[17]

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.[13,18] 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.[19] Lidocaine, lamotrigine, and sulfamethoxazole in its non-reactive form are a few notable examples which directly activate T cells via this pathway.

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.[20] Evidence suggests that unmodified abacavir binds non-covalently to the floor of the peptide binding groove of *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 *HLA-B*57:01*. Hypersensitivity responses are triggered by activation of abacavir-specific T-cells caused by the resultant peptide-centric 'altered self'.[21] There have been suggestions about the possibility that the altered repertoire mechanism is involved in abacavir-induced hypersensitivity and carbamazepine-induced SJS/TEN.[22]

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.[23] 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 anti-convulsants, antiretrovirals, and NSAIDs. SJS/TEN have a high potential for severe morbidity and mortality with TEN having the higher mortality (30-35%).[24]

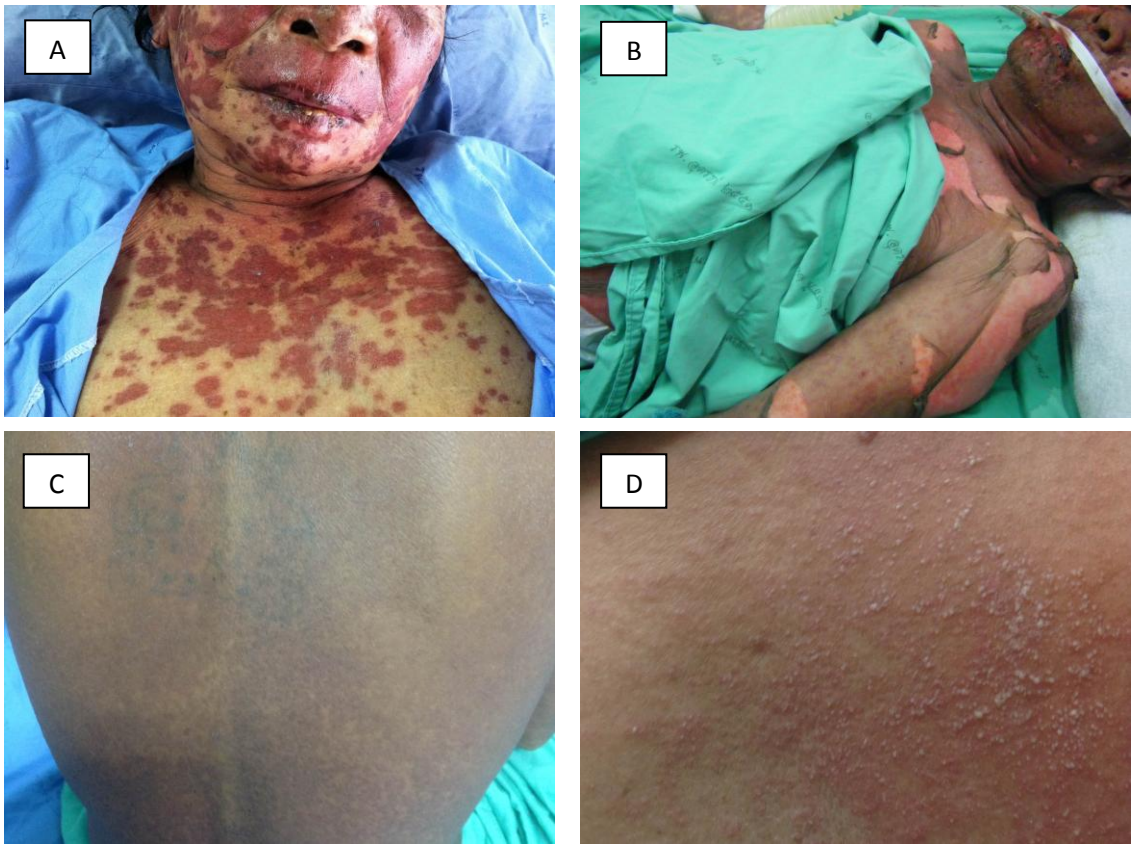

Figure 3. The characteristic features of severe cutaneous adverse drug reactions with (A) Stevens-Johnson syndrome (SJS), (B) toxic epidermal necrolysis (TEN), (C) drug reaction with eosinophilia and systemic symptoms (DRESS), and (D) acute generalized exanthematous pustulosis (AGEP).

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.[25] 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.[26] A fairly diffuse facial edema can appear in patients with DRESS which can be mistaken for angioedema.[27]

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.[26,27]

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.[28] The main adverse event associated with Abacavir treatment is a potentially life-threatening hypersensitivity reaction, commonly referred to 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.[29] 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.[30] 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.[30] As reported by Hetherington et al., *HLA-B57* was present in 39 (46%) of 84 patients versus four (4%) of 113 controls (p <0·0001) in a retrospective, case-control study.[31] Results suggest that the pharmacogenetic results could be used to prevent the adverse reactions of pharmaceuticals.[31] ABC-HSR has shown racial background as a risk factor, with white patients generally having a higher risk than black patients.[32]

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*58:01 (Met45Thr; Ala46Glu; Val97Arg; Val103Leu).[21] 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.[17]

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] A strong association of *HLA-*

*B*15:02* and carbamazepine-induced SJS/TEN has been reported in several studies in Han Chinese populations.[50,54,55] 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= 3.5×10-8)[63] and Japanese (OR:10.8, P=3.64*10^{-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 ancestries 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 anti-convulsant 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. Locharernkul et al. demonstrated the lower cost of screening for *HLA-B*15:02* (27 $US 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.[6,29,75,76] 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, $Pc=4.6x10^{-6}$) and 0.7% in the general Thai population (OR=29.87; $Pc=2.6x10^{-5}$).[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 the SJS/TEN (OR=1.8). In *CYP2B6* T983C SNP, the C allele was significantly associated with a higher risk of developing SJS/TEN (OR4.2, P=0.0047).[81] A recent study by Yuan et al. supports these findings in a case-controlled 11country 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]

Pharmacogenetics of drug-induced hypersensitivity reactions and clinical implementation

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

Figure 4. Pharmacogenetic testing and the pharmacogenomic card have been successfully implemented in clinical practice in Thailand at the Laboratory for Pharmacogenomics, Somdech Phra Debaratana Medical Center, Ramathibodi Hospital. **(A)** "Pharmacogenetic test: *HLA-B* genotyping", with this pharmacogenetic testing, patient 1 and the clinician are informed about the presence of alleles "*HLA-B*58:01/15:02"* as noted on the pharmacogenomic card which will be of benefit in preventing the drug-induced ADRs, if the patientis being considered for treatment with the drugs; allopurinol, carbamazepine, and ox-carbazepine. **(B)** "Pharmacogenetic test: *HLA-B*58:01*", the specific-*HLA-B* marker results are presented for both the heterozygous and homozygous alleles as either "*positive* or *negative*" for the particular *HLA-B* allele. The presence of *HLA-B*58:01/15:02* alleles are reported as "*Positive HLA-B*58:01*" for patient 1. Thus, allopurinol is not recommended for this patient because of the high risk of allopurinol-induced SJS/TEN. The patient and clinician, however, are not informed about the presence of *HLA-B*15:02* in this case. **(C)** Remarkably, *HLA-B*15:02, B*15:08, HLA-B*15:11* and *HLA-B*15:21* belong to the same *HLA-B75* family. Therefore, *HLA-B*15:11* and *HLA-B*15:21* have been reported to be associated with the carbamazepine-induced SJS/TEN. The "Pharmacogenetic test: *HLA-B* genotyping" has been done for patient 2. The patient and clinician are informed about the presence of such alleles as "*HLA-B*15:11/15:21"* on the pharmacogenomic card which will be of benefit in preventing the carbamazepine and ox-carbazepine-induced SJS/TEN for this particular patient. **(D)** Unfortunately, in this case the specific-*HLA-B** marker test, "Pharmacogenetic test: *HLA-B*15:02*", has been ordered for patient 2. The results are presented as "*Negative HLA-B*15:02"*. Consequencely, patient 2 will be treated with the carbamazepine and ox-carbazepine with the high risk of SJS/TEN.

allopurinol are recommended, with *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 *HLA-B*15:02*, and "negative" if no copies of *HLA-B*15:02* are present in the recommendations to prevent carbamazepine-induced SJS/TEN for the carbamazepine therapy.

Conclusion

This review has presented evidence of the genetic associations of drug hypersensitivity reactions with reference to commonly used drugs

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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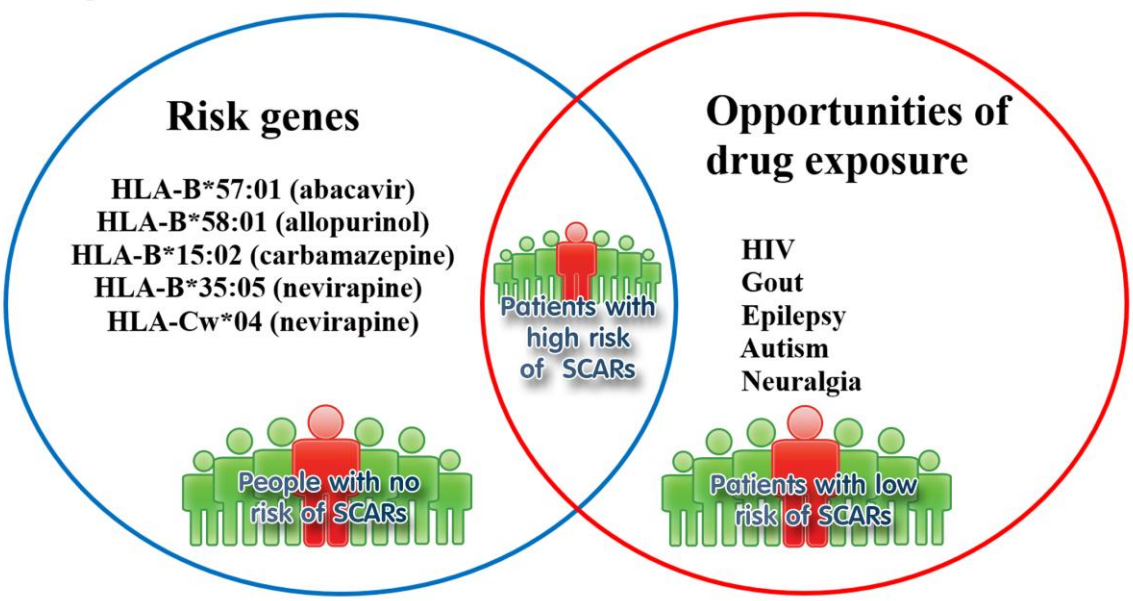

Figure 5. Strong genetic associations of drug-induced SCARs are highlighted. It has to be noted that without the exposure of an individual to the drug, there will be no adverse effects even if an individual carries the risk gene.

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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.

References

1. Naisbitt DJ, Pirmohamed M, Park BK. Immunopharmacology of hypersensitivity reactions to drugs. Curr Allergy Asthma Rep. 2003;3:22-9.
2. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309-16.
3. Roychowdhury S, Svensson CK. Mechanisms of drug-induced delayed-type hypersensitivity reactions in the skin. AAPS J. 2005;7:834-46.
4. Mohamed M. Pharmacogenetics of idiosyncratic adverse drug reactions. Handb Exp Pharmacol. 2010;196:477-91.
5. Descotes J, Choquet-Kastylevsky G. Gell and Coombs's classification: is it still valid? Toxicology. 2001;158:43-9.
6. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. Asia Pac Allergy.2014;4:54-67.
7. Phillips EJ, Mallal SA. Pharmacogenetics of drug hypersensitivity. Pharmacogenomics. 2010;11:973–87.
8. Phillips EJ, Chung W-H, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J Allergy Clin Immunol. 2011;127(3 Suppl):S60-S6.
9. Pichler WJ, editor. Drug hypersensitivity reactions:classification and relationship to T-cell activation. Basel: Karger; 2007: 168-189.
10. Wei CY, Ko TM, Shen CY, Chen YT. A recent update of pharmacogenomics in drug-induced severe skin reactions. Drug Metab Pharmacokinet. 2012;27:132-41.
11. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127:S74-S81.
12. Alfirevic A, Pirmohamed M. Drug induced hypersensitivity and the HLA complex. Pharmaceuticals. 2011;4:69-90.
13. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. Pharmacogenomics. 2012;13:1285.
14. Trowsdale J. The MHC, disease and selection. Immunol Lett. 2011;137:1-8.
15. Hsiao Y-H, Hui RC-Y, Wu T, Chang W-C, Hsih M-S, Yang C-H, et al. Genotype–phenotype association between HLA and carbamazepine-induced hypersensitivity reactions: Strength and clinical correlations. J Dermatol Sci. 2014;73:101–9.
16. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. British J Clin Pharmacol.2011;71:659–71.
17. Bharadwaj M, Illing P, Theodossis A, Purcell AW, Rossjohn J, McCluskey J. Drug hypersensitivity and human leukocyte antigens of the major histocompatibility complex. Annu Rev Pharmacol Toxicol. 2012;52:401-31.
18. Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. Med Clin North Am. 2010;94:645–64.
19. Yun J, Adam J, Yerly D, Pichler WJ. Human leukocyte antigens (HLA) associated drug hypersensitivity: consequences of drug binding to HLA. Allergy. 2012;67:1338–46.
20. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. PNAS. 2012;109:9959–64.
21. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012;486:554-8.
22. Pompeu YA, Stewart JD, Mallal S, Phillips E, Peters B, Ostrov DA. The structural basis of HLA-associated drug hypersensitivity syndromes. Immunol Rev. 2012;250:158-66.
23. Tiwari P, Panik R, Bhattacharya A, Ahirwar D, Chandy A. Toxic epidermal necrolysis: an update. Asian Pacific Journal of Tropical Disease. 2013;3:85-92.
24. Sharma P, Afzal JM. Stevens Johnson Syndrome associated with Lamotrigine. Pak J Med Sci. 2013;29:1450-2.
25. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome. J Am Acad Dermatol. 2013;68:693.e1-.e14.
26. Verma R, Vasudevan B, Pragasam V. Severe cutaneous adverse drug reactions. Medical Journal Armed Forces India. 2013;69:375-83.
27. Khan DA. Cutaneous drug reactions. J Allergy Clin Immunol.. 2012;130(5):1225-.e6.
28. Martin M, Klein T, Dong B, Pirmohamed M, Haas D, Kroetz D. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir Dosing. Clin Pharmacol Ther. 2012;91:734-8.
29. Tozzi V. Pharmacogenetics of antiretrovirals. Antiviral Res. 2010;85:190-200.
30. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;359:727-32
31. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359:1121-2.
32. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis. 2008;46:1111-8.

33. Sun HY, Hung CC, Lin PH, Chang SF, Yang CY, Chang SY, et al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. J Antimicrob Chemother.2007;60:599– 604.
34. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568-79.
35. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis. 2006;43:99-102.
36. Punzi L, Scanu A, Ramonda R, Oliviero F. Gout as autoinflammatory disease: New mechanisms for more appropriated treatment targets. Autoimmun Rev. 2012;12:66-71.
37. Smith HS, Bracken D, Smith JM. Gout: current insights and future perspectives. The J Pain. 2011;12:1113-29.
38. Dallwig R. Allopurinol. Journal of Exotic Pet Medicine. 2010;19:255-7.
39. Engell IA, Authried G. Drug reaction with eosinophilia and systemic symptoms (DRESS) induced by allopurinol: A case report. European Geriatric Medicine. 2013;4:99–101.
40. Thong BYH. Stevens-Johnson syndrome/toxic epidermal necrolysis: an Asia-Pacific perspective. Asia Pac Allergy. 2013;3:215-23.
41. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005;102.
42. Tassaneeyakul W, Jantararoungtong T, Chen P, Khunarkornsiri U, Konyoung P, Choonhakarn C. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics. 2009;19:704-9.
43. Sukasem C, Jantararoungtong T, Rerkpattanapipat T, Prommas S, Koomdee N, Santon S, et al. HLA-B*58:01 allele is strongly associated with allopurinol–induced severe cutaneous adverse reactions in a Thai population. 6th Drug Hypersensitivity Meeting (DHM); European Academy of Allergy and Clinical Immunology (EAACI), Bern, Switzerland. 2014.
44. Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transplant. 2011 Nov;26:3567-72.
45. Goncalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, et al. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens–Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. Br J Dermatol. 2013;169:660–5.
46. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol induced stevens johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet. 2011;12.
47. Tohkin M, Kaniwa N, Saito Y, Sugiyama E, Kurose K, Nishikawa J, et al. A whole-genome association study of major determinants for allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Pharmacogenomics J. 2013;13:60–9.
48. Hershfield M, Callaghan J, Tassaneeyakul W, Mushiroda T, Thorn C, Klein T, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for Human Leukocyte Antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013;93:153-8.
49. Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-Effectiveness Analysis of HLA-B*5801 Testing in Preventing Allopurinol-Induced SJS/TEN in Thai Population. PLOS ONE. 2014;9:e94294.
50. Wang Q, Zhou J-q, Zhou L-m, Chen Z-y, Fang Z-y, Chen S-d, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. Seizure. 2011;20:446-8.

Reference 51-82 are available online

51. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010;5.
52. Ferrell PB Jr, McLeod HL.Carbamazepine, HLA-B*1502 and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9:1543-6.
53. Leckband S, Kelsoe J, Dunnenberger H, Jr AG, Tran E, Berger R, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013;94:324-8.
54. Shi Y-W, Min F-L, Qin B, Zou X, Liu X-R, Gao M-M, et al. Association between HLA and Stevens–Johnson Syndrome induced by carbamazepine in Southern Han Chinese: genetic markers besides B*1502? Basic Clin Pharmacol Toxicol. 2012;111:58–64.
55. Zhang Y, Wang J, Zhao L-M, Peng W, Shen G-Q, Xue L, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. Eur J Clin Pharmacol. 2011;67:885–7.
56. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol. 2009;75:579-82.
57. Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Prabmechai N, Vannaprasaht S, et al. HLA-B*1502 strongly predicts carbamazepine-induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis in Thai patients with neuropathic pain. Pain Pract. 2012;12:202-8.
58. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B∗1502 allele in Thai population. Epilepsia. 2008;49:2087–91.
59. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepineinduced toxic epidermal necrolysis and Stevens–Johnson syndrome in the multi-ethnic Malaysian population. Int J Dermatol. 2011;50:221–4.
60. Chong KW, Chan DWS, Cheung YB, Ching LK, Hie SL, Thomas T, et al. Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B*1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore. Arch Dis Child. 2013.
61. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin S-Y, Chen W-H, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia. 2010;51:926-30.
62. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011; 24;364(12):1126-33.
63. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperaviciute D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364:1134–43.
64. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet. 2011;20:1034-41.
65. Amstutz U, Ross C, Castro-Pastrana L, Rieder M, Shear N, Hayden M, et al. HLA-A*31:01 and HLA-B*15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Ther. 2013;94:142-9.
66. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006;16:297-306.
67. Kim S-H, Lee KW, Song W-J, Kim S-H, Jee Y-K, Lee S-M, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res. 2011;97:190-7.
68. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia. 2010;51:2461–5.
69. Wei C-Y, Chung W-H, Huang H-W, Chen Y-T, Hung S-I. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. J Allergy Clin Immunol. 2012;129:1562-9.
70. Aihara M. Pharmacogenetics of cutaneous adverse drug reactions. J Dermatol. 2011;38:246-54.
71. Wang XQ, Lang SY, Shi XB, Tian HJ, Wang RF, Yang F. Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. Seizure. 2010;19:562-6.
72. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RCy, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics. 2010;11:349-56.
73. Locharernkul C, Shotelersuk V, Hirankarn N. HLA-B* 1502 screening: time to clinical practice. Epilepsia. 2010;51:936-8.
74. Tiamkao S, Jitpimolmard J, Sawanyawisuth K, Jitpimolmard S. Cost minimization of HLA-B*1502 screening before prescribing carbamazepine in Thailand. Int J Clin Pharm. 2013;35:608–12.
75. Junior HP, Gosuen GC, Gales AC. DRESS syndrome due to nevirapine treated with methylprednisolone. Case Rep Med. 2013;2013.
76. McKoy JM, Bennett CL, Scheetz MH, Differding V, Chandler KL, Scarsi KK, et al. Hepatotoxicity associated with long-versus short-course hiv- prophylactic nevirapine use:a systematic review and meta-analysis from the research on adverse drug events and reports (radar) project. Drug Saf. 2009;32:147–58.
77. Bourezane Y, Salard D, Hoen B, Vandel S, Drobacheff C, Laurent R. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome associated with nevirapine therapy. Clin Infect Dis. 1998;27:1321-2.
78. Likanonsakul S, Rattanatham T, Feangvad S, Uttayamakul S, Prasithsirikul W, Tunthanathip P, et al. HLA-Cw*04 allele

associated with nevirapine-induced rash in HIV-infected Thai patients. AIDS Res Ther. 2009;6.

79. Gao S, Gui XE, Liang K, Liu Z, Hu J, Dong B. HLA-dependent hypersensitivity reaction to nevirapine in Chinese Han HIV-infected patients. AIDS Res Hum Retroviruses. 2012;28:540-3.
80. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, Manosuthi W, et al. HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenet Genomics 2009;19:139-46.
81. Ciccacci C, Fusco DD, Marazzi MC, Zimba I, Erba F, Novelli G, et al. Association between CYP2B6 polymorphisms and Nevirapine-induced SJS/TEN: a pharmacogenetics study. Eur J Clin Pharmacol. 2013;69:1909-16.
82. Yuan J, Guo S, Hall D, Cammett AM, Jayadev S, Distel M, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. AIDS. 2011;25:1271-80.