

INVITED ARTICLE

Pharmacogenetics of cutaneous adverse drug reactions

Michiko AIHARA

Department of Dermatology, Yokohama City University School of Medicine, Yokohama, Japan

ABSTRACT

Drug-induced hypersensitivity reactions are of major medical concern because they are associated with high morbidity and high mortality. In addition, individual patients' reactions are impossible to predict in each patient. In the field of severe cutaneous adverse drug reactions (cutaneous ADR) such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DHIS) or drug rash with eosinophilia and systemic symptoms (DRESS), major advances have recently been gained through studies of an association between HLA alleles and drug hypersensitivity induced by specific drugs. The results of these pharmacogenomic studies allow prediction of the risk of adverse reactions in patients treated with certain drugs, including carbamazepine and other aromatic antiepileptic drugs, allopurinol and abacavir. However, different ethnic populations show variations in the genetic associations. A strong association between carbamazepine-induced SJS/TEN and HLA-B*1502 has been found in Southeast Asian patients but not in Caucasian and Japanese patients. Moderate associations between aromatic amine anticonvulsants and other HLA alleles have been proposed in Japanese patients. In contrast, HLA-B*5801 was found to be associated with allopurinol-induced cutaneous ADR, including SJS/TEN and DHIS/DRESS, in Caucasian and Asian patients, including the Japanese. These differences may, at least in part, be due to the differences in allele frequency in different ethnic populations. This article reviews the progress in pharmacogenomics, associated mainly with carbamazepine and allopurinol in different ethnic populations. Pharmacogenetic screening based on associations between adverse reactions and specific HLA alleles helps to avoid serious conditions associated with drug hypersensitivity.

Key words: adverse drug reaction, drug-induced hypersensitivity syndrome, pharmacogenetics, Stevens–Johnson syndrome, toxic epidermal necrolysis.

INTRODUCTION

Drug hypersensitivities develop in susceptible patients as adverse drug reactions (ADR) following exposure to certain drugs. Many of the ADR are thought to be immunologically mediated and are of major concern to clinicians, because severe hypersensitivity is life-threatening and cannot be predicted.

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are major cutaneous ADR

characterized by destruction of the epidermis and mucosal epithelium, often with organ involvement. They are considered variants of the same disorder differentiated by the presence of skin separation and extent of the body surface area involved.^{1,2} Although they are rare disorders, the mortality is as high as 1–5% for SJS and 20–30% for TEN.^{3,4} Common drugs that cause SJS/TEN include allopurinol, anticonvulsants, antimicrobials, non-steroidal anti-inflammatory agents and aromatic sulphonamide, although many other drugs can be implicated in SJS/TEN.

Correspondence: Michiko Aihara, M.D., Department of Dermatology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: maihara1@med.yokohama-cu.ac.jp
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Drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) are other severe cutaneous ADR. In patients with DIHS/DRESS, skin rash usually occurs more than 2 weeks after the initial administration of the drug, associated with fever, hepatitis and/or other internal organ involvement, lymphadenopathy and hematological abnormalities (leukocytosis, hyper-eosinophilia and atypical lymphocytosis). Reactivation of human herpesvirus (HHV), mainly HHV-6, and less frequently cytomegalovirus, has been described during the course of DIHS/DRESS.⁵⁻⁸ These viral reactivations have been reported in association with recurrence of symptoms more than 2 weeks after the drug was discontinued.^{7,8} Common drugs associated with DIHS/DRESS include aromatic amine anticonvulsants (carbamazepine, phenytoin and phenobarbital), allopurinol, minocycline, sulfa antimicrobials and aromatic sulfonamides.

Not only immunological but also genetic factors have recently been suggested to contribute to the pathogenesis of cutaneous ADR. This notion is supported by studies associating human leukocyte antigen (HLA) class I alleles with SJS/TEN induced by anticonvulsants. In addition to playing a role as a genetic marker for cutaneous ADR, the particular HLA molecule is also functionally involved in the pathogenesis of cutaneous ADR. The drug antigen (e.g. drug-peptide complex) is presented by the specific HLA molecule on the antigen-presenting cells and recognized by effector T cells through the T-cell receptor for HLA-restricted T-cell activation. HLA class I restricted CD8⁺ T cells and HLA class II restricted CD4⁺ T cells are thought to induce an immune response, including cutaneous ADR. In SJS/TEN, CD8⁺ cytotoxic T cells in the skin lesions may play an important role in eliciting keratinocyte death.⁹

In 2004, a very strong association of HLA-B*1502 with carbamazepine-induced SJS/TEN was reported in southeast Asian patients¹⁰⁻¹² and patients of Asian ancestry living in Europe.¹³ This was an epoch-making finding in the field of pharmacogenetics of cutaneous ADR. However, the association has not shown across different populations or ethnicities. Moderate associations between aromatic amine anticonvulsants and other HLA alleles have been proposed in different ethnic populations. In contrast, some studies

showed an association between the HLA class I allele and allopurinol-induced ADR, including TEN/SJS and DIHS/DRESS, across different populations.^{14,15}

This review is focused on the recent pharmacogenetic studies of cutaneous ADR, including TEN/SJS and DIHS/DRESS, mainly induced by carbamazepine and allopurinol, and hypersensitivity induced by antiretroviral drugs, and discusses future perspectives of pharmacogenomics in cutaneous ADR.

ALLELE ASSOCIATIONS WITH CUTANEOUS ADR INDUCED BY AROMATIC AMINE ANTICONVULSANTS

Recently, many studies on allele associations with cutaneous ADR induced by aromatic amine anticonvulsants have been reported in Asian and European populations. Current studies indicate that HLA-B*1502 is a marker for carbamazepine-induced SJS/TEN in southeast Asian populations, where the prevalence of HLA-B*1502 is relatively high.

ASSOCIATION BETWEEN HLA-B*1502 AND CARBAMAZEPINE-INDUCED SJS/TEN IN SOUTHEAST ASIAN AND EUROPEAN PATIENTS

In 2004, Chang *et al.*¹⁰ reported a strong association between HLA-B*1502 and carbamazepine-induced SJS/TEN in Han-Chinese residing in Taiwan (Table 1). In this case-control study, 100% of 44 Han-Chinese SJS/TEN patients were HLA-B*1502 positive versus 3% of 101 tolerant patients and 8.6% in the general population ($P = 3.1 \times 10^{-27}$; odds ratio [OR] = 2505).¹⁰ A follow-up study by Hung *et al.*¹⁶ confirmed this association not only in Han-Chinese residing in Taiwan but also in those residing in Hong Kong and China and in Chinese descendants residing in the USA (98.3% of 60 patients, $P = 1.6 \times 10^{-41}$; OR = 1357). Further studies have confirmed the association between HLA-B*1502 and carbamazepine-induced SJS/TEN in Chinese, Thai and Indian populations.^{11,12,17} Tassaneeyakul *et al.*¹⁸ have performed a case-control study using 42 carbamazepine-induced SJS/TEN patients and 42 carbamazepine-tolerant controls in a Thai population. In their study, 37 SJS/TEN patients carried HLA-B*1502, thus suggesting a very strong association of HLA-B*1502 with

Table 1. Reported genetic biomarkers for anticonvulsants-induced cutaneous ADR

Causative drug	HLA-B	Race		Selectivity	References
Carbamazepine	*1502	Han Chinese (Taiwan)	SJS/TEN	59/60	16
		Han Chinese (Hong Kong)	SJS/TEN	4/4	11
		Asians in Europe	SJS/TEN	4/4	13
		Thai	SJS	37/42	18
		Indians	SJS	6/8	17
		Caucasians	SJS/TEN	0/8	13
		Japanese	SJS/TEN	0/15	22
		Han Chinese (Taiwan)	DIHS	0/13	16
		Caucasians	DIHS	0/56	29
		Japanese	SJS/TEN	4/15	22
Phenytoin	*1511	Japanese	SJS/TEN	4/15	22
	*1502	Han Chinese (Taiwan)	SJS/TEN	8/26	28
Lamotrigine	*1502	Thai	SJS/TEN	4/4	18
		Han Chinese (Taiwan)	SJS	2/6	28
Oxcarbazepine		Han Chinese (Taiwan)	SJS	3/3	28

ADR, adverse drug reactions; HLA, human leukocyte antigen; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

SJS/TEN ($P = 2.89 \times 10^{-12}$; OR = 54.76). In India, the same association was shown in six out of eight patients by Mehta *et al.*¹⁷

In contrast, this association has not been detected in Caucasian populations.¹⁹ A European study performed by Lonjou *et al.*¹⁹ included 12 carbamazepine-induced SJS/TEN patients, four HLA-B*1502-positive patients who had Asian ancestry and eight HLA-B*1502-negative Caucasian patients. These studies demonstrate that an association between HLA-B*1502 and carbamazepine-induced SJS/TEN is observed only in southeast Asian populations.

ALLELE ASSOCIATIONS WITH CARBAMAZEPINE-INDUCED SJS/TEN IN JAPANESE PATIENTS

In Japanese studies, none of the SJS/TEN patients receiving aromatic anti-epileptic drugs, including carbamazepine, carried HLA-B*1502 (Table 1).^{20–23} Ueta *et al.* reported a case–control study on the relationships between HLA class I and II genetic polymorphisms with severe ocular complications using 71 Japanese drug-unspecified SJS/TEN patients and 101 Japanese controls. No HLA-B*1502 carriers were detected in cases or controls.²⁴ Instead, the investigators reported that HLA-A*0206 was associated with SJS/TEN with severe ocular complications ($P = 4 \times 10^{-5}$; OR = 4.1).²⁴

Recently, our group detected four patients carrying HLA-B*1511 among 15 carbamazepine-induced

SJS/TEN patients (26.7%). The allele frequency of HLA-B*1511 was significantly increased in the patients (13.3%) compared with that of the Japanese population (1%) ($P < 10^{-4}$; OR = 19.52).²² These data suggest that HLA-B*1511, a member of the HLA-B75 group, as well as HLA-B*1502, are risk factors for carbamazepine-induced SJS/TEN in Japanese populations. Other major members of HLA-B75 are HLA-B*1508, HLA-B*1515 and HLA-B*1521. Interestingly, HLA-B*1508, HLA-B*1511 and HLA-B*1521 were detected in studies on SJS/TEN in Thailand and India.^{12,17} These findings suggest that subfamilies belonging to the HLA-B75 serotype are involved in carbamazepine-induced SJS/TEN.

ALLELE FREQUENCIES OF INDIVIDUAL HLA-B75 (B*1502, B*1508, *1511, B*1515, B*1521) GENOTYPES

Allele frequencies of individual HLA genotypes in worldwide populations are shown at www.allele-frequencies.net (Table 2).²⁵ The prevalence of HLA-B*1502 is relatively high in southern Chinese and southeast Asian populations where HLA-B*1502 is in fact a marker for carbamazepine-induced SJS/TEN.²² In contrast, the prevalence of HLA-B*1502 is very low in Caucasian and Japanese populations. This suggests that one reason for not detecting HLA-B*1502 in carbamazepine-induced SJS/TEN in Japanese and Caucasian patients is the low allele frequency. In addition, the extremely low allele frequencies of HLA-B75 subfamilies in Caucasians

Table 2. Population allele frequencies of major subfamilies of serotype B75

Ethnic group	Population allele frequencies reported in www.allelefrequencies.net website [†]				
	HLA-B*1502	HLA-B*1515	HLA-B*1521	HLA-B*1508	HLA-B*1511
Japanese	0.001				0.004–0.008 [‡]
Koreans	0.002	0	0	0	0.02
Han Chinese	0.019–0.124	0.01	0.000–0.002	0.005–0.015	0.000–0.017 [§]
Thai	0.061–0.085		0.007–0.010	0.01	0.01
Indians	0.000–0.060			0.005–0.033	
Caucasians	0	0	0	0.000–0.004	0.000–0.003

[†]New Allele Frequency Database: www.allelefrequencies.net/ (Middleton *et al.*).²⁵ [‡]The frequency of 0.1 was reported by Tanaka *et al.*⁴⁵ [§]Higher value than 0.038 in Han Chinese in Beijing was recently reported by Yang *et al.*⁴⁶ This table was partly quoted from Kaniwa *et al.*²² HLA, human leukocyte antigen.

may be a reason for detecting no HLA-B75 subfamilies, including HLA-B*1511, in the Caucasian patients with carbamazepine-induced SJS/TEN.

HLA-B ASSOCIATION IN OTHER AROMATIC AMINE ANTICONVULSANT-INDUCED SJS/TEN

Aromatic amine anticonvulsants such as carbamazepine, phenytoin, phenobarbital, oxcarbazepine and lamotrigine are metabolized to arene oxide metabolites. Clinical cross-reactivity among aromatic amine anticonvulsants is observed with high frequency.^{26,27} Small case studies in Thailand (four cases phenytoin induced) and Hong Kong (single cases of phenytoin and lamotrigine induced) showed the presence of HLA-B*1502 in all SJS patients.^{11,12} In a current case–control association study in a Taiwanese population, the association between HLA-B*1502 and phenytoin-, lamotrigine- and oxcarbazepine-induced SJS/TEN was observed in 30.8% of 26 patients ($P = 4.1 \times 10^{-3}$; OR = 5.1), 33% of six patients ($P = 1.3 \times 10^{-1}$; odds ratio = 5.1) and 100% of three patients ($P = 8.4 \times 10^{-4}$; OR = 80.7), respectively.²⁸ These results indicate that aromatic anticonvulsants share a common risk allele, HLA-B*1502, presumably by similar antigen recognition, although the association is highest with carbamazepine. Other genetic factors may also contribute to the pathomechanism of the disease. Thus, HLA-B*1301, Cw*0801 and DRB1*1602 also showed an association with phenytoin-SJS/TEN in the same study ($P = 0.0128$ – 0.0281 ; OR = 3.0–4.3).²⁸

In Europe, where the allele frequency of HLA-B*1502 is extremely low, a rare allele, HLA-B*38, showed a weaker association ($P < 2 \times 10^{-2}$;

OR = 6.8) with SJS/TEN in a limited number of patients treated with lamotrigine.¹⁵

ALLELE ASSOCIATIONS WITH DIHS/DRESS AND MACULOPAPULAR ERUPTION INDUCED BY AROMATIC AMINE ANTICONVULSANTS

In addition to SJS/TEN, carbamazepine also induces other types of cutaneous ADR, including maculopapular eruption (MPE) and DIHS/DRESS. The association between HLA-B*1502 and carbamazepine-induced MPE was not detected in Han-Chinese populations in Taiwan and Hong Kong or in the Thai population.^{11,12,16} Studies in 18 Han-Chinese patients residing in Taiwan and 56 Caucasian patients showed that carbamazepine-induced DIHS/DRESS was not associated with HLA-B*1502.^{16,29} These data suggest that the association between HLA-B*1502 and carbamazepine-induced cutaneous ADR is specific to SJS/TEN.

Kano *et al.*³⁰ showed that four out of 13 Japanese patients (30.8%) with DIHS/DRESS – all associated with HHV-6 reactivation – induced by aromatic amine anticonvulsants (carbamazepine, eight; phenobarbital, two; phenytoin, one) had HLA-B*1301 (allele frequency 15.4%). This allele frequency of HLA-B*1301 was much higher than that reported for the Japanese population (1.3%),³¹ although the difference was not statistically significant after correction for multiple comparisons. They supposed that the effect of certain HLA-B alleles on the virus reactivation contributed, in part, to the HLA-B allele association with DIHS/DRESS.

Recently, we found a significant association between carbamazepine-induced cutaneous ADR

and HLA-A*3101 in 22 Japanese patients, including MPE, erythema multiforme, erythroderma, DIHS, SJS and other types. Eleven patients (50%), including two SJS patients and others, carried HLA-A*3101, and the allele frequency was much higher in the patients (25%) than that reported for the Japanese population (7.1%) ($P = 4 \times 10^{-4}$; OR = 4.33).²³ Another study involving carbamazepine-induced MPE in 18 Han-Chinese also suggested the association with HLA-A*3101 ($P = 2.2 \times 10^{-4}$; OR = 17.5).¹⁶ The sample sizes of these studies were small, so further study on a large sample size is needed to clarify whether or not HLA-A*3101 is a risk allele.

ASSOCIATION BETWEEN HLA-B*5801 AND ALLOPURINOL-INDUCED CUTANEOUS ADR

Allopurinol is a xanthine oxidase inhibitor used to treat gout and hyperuricemia (Table 3). A case-control study in a Han-Chinese population showed an extremely strong association between HLA-B*5801 and allopurinol-induced SJS/TEN or DIHS/DRESS.¹⁴ In this study, all 51 patients (100%) with allopurinol-induced SJS/TEN or DIHS/DRESS carried HLA-B*5801, compared with only 20 out of 135 (15%) allopurinol-tolerant patients and 19 out of 93 (20%) population controls ($P < 10^{-6}$; OR = 580). Regarding the association in other southeast Asian populations, a similar strong association between HLA-B*5801 and allopurinol-induced SJS/TEN was shown in a case-control study in a Thai population.³²

The association of HLA-B*5801 with allopurinol-induced SJS/TEN was observed in a European study as well ($P < 10^{-8}$; OR = 80).¹⁵ The carrier frequency was 55% in 27 European patients. One of the reasons for the lower carrier frequency seems to be the lower

allele frequency of HLA-B*5801 (1–6%) in the European population than in southeast Asian populations, although HLA-B*5801 is more broadly distributed than HLA-B*1502.

In the Japanese population, the allele frequency of HLA-B*5801 is less than 1%.²⁰ We have reported earlier that four out of 10 Japanese patients (40%) with allopurinol-induced SJS/TEN carried HLA-B*5801.²⁰ A moderate but statistically significant association ($P < 10^{-4}$, OR = ~40) between HLA-B*5801 and allopurinol-induced SJS/TEN was detected in that study. Our recent data have shown that 10 out of 18 Japanese patients (55.6%) with allopurinol-induced SJS/TEN carried HLA-B*5801 (M. Tohkin, unpubl. data, 2010). Dainichi *et al.*³³ also detected three HLA-B*5801 carriers in all three allopurinol-treated Japanese patients diagnosed with SJS, DIHS and TEN, respectively. Although the sample size in our study was not sufficient to estimate the accurate carrier frequency in Japanese patients, it showed a possible association between HLA-B*5801 and allopurinol-induced SJS/TEN in Japan.

These studies lead to the conclusion that HLA-B*5801 is a potential genetic biomarker for allopurinol-associated SJS/TEN across different populations or ethnicities, although there is less information regarding the association in other populations than the Japanese.

ALLELE ASSOCIATION WITH CUTANEOUS ADR INDUCED BY ANTIRETROVIRAL DRUGS

HIV patients treated with antiretroviral drugs show a high frequency of cutaneous ADR, including SJS/TEN and hypersensitivity syndrome (Table 4). The hypersensitivity syndrome is associated with fever,

Table 3. Reported genetic biomarkers for allopurinol-induced cutaneous ADR

HLA-B	Race	ADR	Selectivity	References
*5801	Han Chinese (Taiwan)	SJS/TEN or DIHS/DRESS	51/51	14
	Thai	SJS/TEN	27/27	32
	Caucasians	SJS/TEN	15/27	15
	Japanese	SJS/TEN/DIHS	3/3	33
	Japanese	SJS/TEN	4/10	20

ADR, adverse drug reactions; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 4. Reported genetic biomarkers for cutaneous ADR induced by antiretroviral drugs

Causative drug	HLA	Race	ADR	Selectivity	References
Abacavir	B*5701	Caucasians	Hypersensitivity	57/130	40
			Hypersensitivity (patch test+)	42/42	40
		Black	Hypersensitivity	10/69	40
			Hypersensitivity (patch test+)	5/5	40
			Hypersensitivity	0/7	38
Nevirapine	B*3505	Japanese	Hypersensitivity	25/143	42
		Thai	Hypersensitivity	5/12	44
	Cw8	Japanese	Hypersensitivity	6/3	43
	Cw8	Sardinian	Hypersensitivity	6/13	43
	B14	Sardinian	Hypersensitivity		

ADR, adverse drug reactions; HLA, human leukocyte antigen.

rash and internal organ involvement (gastrointestinal symptoms in abacavir-treated patients and hepatitis in nevirapine-treated patients).³⁴

ABACAVIR

Abacavir is a guanosine analog that belongs to the family of nucleoside reverse transcriptase inhibitors used for treatment of HIV infection. Hypersensitivity to abacavir occurs in approximately 5–8% of patients within 1–6 weeks of the initial dose.³⁵ The initial association between abacavir-induced hypersensitivity and HLA-B*5701 was reported in Australian and British populations.^{36,37} However, abacavir-induced hypersensitivity is present at a high frequency only in Caucasians and at a very low frequency in Asian and black populations.^{38,39} In fact, the allele frequency of HLA-B*5701 is approximately 8% in Caucasians, but lower in Asian and African populations.^{36,37} To examine the universality of the sensitivity and specificity of HLA-B*5701 association with abacavir hypersensitivity across ethnicities, the Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) was performed. It was a case-control study that enrolled both white and black patients in the USA.⁴⁰ This study showed that 100% of both white and black patch test-positive patients carried HLA-B*5701, suggesting a predictive value of HLA-B*5701 for abacavir-induced hypersensitivity across ethnicities. This study demonstrated the clinical utility of testing for HLA-B*5701 prior to prescription of abacavir.

Although all current studies show the requirement for HLA-B*5701 presence for development of abacavir-induced hypersensitivity syndrome, 45% of

patients who carry HLA-B*5701 do not develop the hypersensitivity syndrome.⁴¹ Therefore, it is likely that HLA-B*5701 is necessary but not sufficient for development of abacavir-induced hypersensitivity syndrome.

NEVIRAPINE

Nevirapine is another antiretroviral agent that is a potent non-nucleoside reverse transcriptase inhibitor. Nevirapine often causes cutaneous ADR with a frequency of approximately 5% for hypersensitivity syndrome and 0.3% or less for SJS/TEN.³⁴ A recent case-control study in Thailand showed a high frequency of HLA-B*3505 (17.5%) in patients with nevirapine-induced hypersensitivity syndrome.⁴² Because HLA-B*3505 is carried by less than 1% of the Thai population, a strong association between HLA-B*3505 and nevirapine-induced hypersensitivity syndrome is suggested. HLA-Cw8 and HLA-B*1402 associations with nevirapine-induced hypersensitivity were also reported in a Sardinian population,⁴³ and a HLA-Cw8 association was noted in a Japanese population.⁴⁴ To date, no specific HLA association has been described in nevirapine-induced SJS/TEN.

FUTURE PERSPECTIVE OF PHARMACOGENOMICS IN CUTANEOUS ADR

Elucidation of associations between HLA alleles and drug hypersensitivity will make it possible to predict immunologically mediated drug reactions and prevent them in the future. As a result of current studies, the strong associations between HLA-B*1502 and

carbamazepine-induced SJS/TEN in patients of Asian ancestry, and between HLA-B*5701 and abacavir hypersensitivity, have been included in the labels on these drugs, and screening for these alleles is recommended by the US Food and Drug Administration (FDA) prior to initiating therapy with these drugs. The FDA has also updated the genetic information on other drug labels and now recommends genetic testing for more than 10 drugs. In order to perform a widespread genetic screening for these drugs, technology advancement is needed to decrease the cost of the screening. It is to be hoped that pharmacogenetic testing kits will be available in the near future for prevention of severe reactions such as SJS/TEN and hypersensitivity syndrome. In addition, the ability to predict the propensity of drugs to cause ADR will make pharmacogenomic screening an important tool in new drug development in the future.

Although strong associations have been shown between HLA alleles and some types of cutaneous ADR, there has been no definitive proof or data published concerning the functions of the implicated HLA alleles. HLA-restricted T-cell activation is needed for induction of immunological reactions and, in addition, there is a possibility that some HLA proteins have higher binding affinity than others toward a drug or drug metabolite through covalent or non-covalent mechanisms. On the other hand, a protecting effect of HLA has been suggested. Alfirevic *et al.*²⁹ reported a potential protecting effect of HLA-B*0702 against carbamazepine-induced severe cutaneous adverse reactions in Caucasian patients. Functional studies together with genomic approaches are required for further progress in understanding the pathogenesis of ADR.

Many questions are still unresolved. For instance, it is still unclear what the genetic difference is between the patients who develop severe reactions such as SJS/TEN and milder skin reactions, and between the patients who develop severe skin reactions and those who have only internal organ involvement with the same drug. In order to elucidate the pathogenesis of these diseases, definite case-control studies will be needed.

For further development of pharmacogenomics, collaboration between different research groups is needed to collect larger numbers of biological

samples from ADR patients, particularly from those with rare ADR such as SJS/TEN. This association is also needed across ethnicities, based on consistent definitions of diseases.

CONCLUSIONS

Studies presented in this review show the tremendous progress in the area of pharmacogenetics of cutaneous ADR in recent years. It is likely that further progress will be made in this field by the continuous development of genetic technologies and the international well-defined sampling of the patients. This could result in the reduction of serious cutaneous ADR by screening prior to initiating drug therapies. Further studies, such as confirmatory haplotype-mapping, are required to definitively identify the susceptibility region responsible for the hypersensitivity.

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