

Genetic and ethnic risk factors associated with drug hypersensitivity

Seung-Hyun Kim, Young-Min Ye, Nami Shrestha Palikhe, Jeong-Eun Kim and Hae-Sim Park

Department of Allergy & Rheumatology, Ajou University School of Medicine, Suwon, South Korea

Correspondence to Dr Hae-Sim Park, MD, PhD, Professor, Department of Allergy and Rheumatology, Ajou University Hospital, Yongtonggu Woncheondong San-5, 443-721 Suwon, South Korea
Tel: +82 31 219 5196; fax: +82 31 219 5154;
e-mail: hspark@ajou.ac.kr

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Purpose of review

The purpose of this article is to review the recent findings of studies reporting on the genetic and ethnic factors associated with hypersensitivity reactions to common drugs such as acetyl salicylic acid/NSAIDs, antibiotics, antituberculous medications, and other drugs including carbamazepine (CBZ), abacavir, and allopurinol that can cause severe hypersensitivity reactions.

Recent findings

Aspirin hypersensitivity has recently been associated with a variety of genetic polymorphisms associated with leukotriene overproduction, eosinophil infiltration, and histamine-related genes. Recently, β -lactam antibiotic hypersensitivity has been reported to be associated with interleukin (IL)-4 and IL-13 receptors in Italian, Chinese, and French populations. Moreover, a significant association of CYP2E1 in the Chinese, NAT2 in Koreans and glutathione S-transferase genotypes in Caucasians has been reported with antituberculous drug-induced hepatitis. The association of the HLA-B*1502 allele with CBZ-induced Stevens–Johnson syndrome in Asian population has also recently been observed.

Summary

Aspirin hypersensitivity has been associated with various genetic polymorphisms. Human leukocyte antigen (HLA)-related markers and a variety of genetic polymorphisms of leukotriene-related genes, eosinophil-related genes, and genes associated with immune function have been described according to ethnicity. The genetic mechanisms of antibiotic hypersensitivity have been reported in Italian, French, and Chinese populations in addition to antibiotics-induced cutaneous reactions in the Korean population. Most prior genetic studies on antituberculous drug-induced hepatitis have focused on a few drug-metabolizing enzymes such as cytochrome P450 and *N*-acetyltransferase 2. HLA-related markers associated with CBZ, lamotrigine, and abacavir-induced severe hypersensitivity reactions have been described.

Keywords

antibiotics, anticonvulsant agent, antitubercular agent, aspirin, drug hypersensitivity

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Introduction

Drug hypersensitivity reactions may be immune- or not immune-mediated unpredictable adverse events that account for about 15% of hospitalized patients and occur in more than 7% of the general population [1,2]. These adverse drug reactions commonly involve the skin and mucosal surfaces, and in severe cases can lead to hepatitis, renal failure, gastrointestinal bleeding, pneumonitis, bone marrow suppression, and death [3]. The frequency, severity, and clinical manifestations vary according to the drug, the underlying disease, and the ethnicity of the patient.

Drug hypersensitivity is regarded as a multifactorial and multigenic process involving drug metabolism and immune responses that are dependent on a complex interaction between environmental and genetic factors [4]. Environmental factors such as age, sex, alcohol intake, preexisting disease, and viral infections are important risk factors. The genetic factors are associated with the genes that influence drug metabolism and/or the immunological reactions to the drug.

Using pharmacogenetic investigations, many genetic factors have been identified as predisposing factors associated with drug hypersensitivity. Most pharmacogenetic

studies of drug hypersensitivity have been performed by the candidate gene approach of drug metabolism-related genes. Recently, genome-wide approach using single nucleotide polymorphism (SNP) microarray has been employed to detect associations between SNPs and drug-induced liver injury due to flucloxacillin [5].

The focus of the present review is on adverse reactions caused by frequently used drugs including aspirin (ASA), antibiotics, antituberculous medications, and anticonvulsant agents, underlying genetic factors for each drug with ethnic differences.

The genetic mechanism associated with acetyl salicylic acid/NSAIDs hypersensitivity

Aspirin (acetyl salicylic acid; ASA) and other NSAIDs hypersensitivity is a major cause of adverse drug reactions. The two main phenotypes associated with these adverse events are aspirin exacerbated respiratory disease (AERD) and aspirin intolerant urticaria (AIU). AERD is defined by the clinical syndrome that is associated with moderate to severe asthma and eosinophil inflammation in the upper and lower airways resulting in chronic rhino-sinusitis and asthma [6]. The prevalence of ASA hypersensitivity in the general population ranges from 0.6 to 2.5% and in the population of persons with asthma, 10–20% have been reported to develop AERD [7], with no racial or ethnic predilections. AIU has been divided into two subgroups on the basis of severity and duration of the urticaria: aspirin-intolerant acute urticaria (AIAU) and aspirin-intolerant chronic urticaria (AICU). The key pathogenic mechanisms

associated with AERD are over production of cysteinyl leukotrienes (CysLTs) and increased CysLTR1 expression in the airway mucosa [8] with decreased lipoxin and PGE2 synthesis [9]; however, the mechanisms associated with AIU remain to be elucidated [10].

Genetic studies of aspirin exacerbated respiratory disease

Leukotriene-related genes

The initial investigations focused on the genes involved in the synthetic pathway of CysLTs, since the C allele of the *LTC4* –444A>C promoter polymorphism was identified as a risk factor for AERD in a Polish population [11] (Table 1). However, these findings were not replicated in Japanese, American, and Korean populations [20–22]. Recently, three SNPs (–634C>T, –475A>C, and –336A>G) in the promoter region of *CysLTR1* were identified and the mutant variants of these three SNPs were associated with the AERD phenotype [12] and increased expression of CysLTR1 in peripheral mononuclear cells in the Korean population [22]. In addition, a study performed in the Korean population showed that the frequencies of the rare alleles for –819T>G, 2078C>T, 2534A>G of *CysLTR2* were significantly higher in the AERD group [13], which were also noted in Caucasian [23] and Japanese populations [24].

Cyclooxygenase, prostanoid genes, and human leukocyte antigen markers

A *COX2* promoter polymorphism at –765G>C was identified in a Polish population [15] that showed a significant association with sex, atopy, and increased prostaglandin

Table 1 Genetic and ethnic risk factors in aspirin exacerbated respiratory disease

Drug	Phenotype	Gene	Full name	Genotype	Association	Population	Sample size	Year	Reference
Leukotrienes-related gene									
Aspirin	AERD	LTC4S	Leukotriene C4 synthase gene	C allele of A–444C	Y	Polish	60 AERD, 100 ATA, 110 NC	2000	[11]
Aspirin	AERD	CysLTR1	Cysteinyl leukotriene receptor1	Mutant construct – 634C>T, –475A>C and –336A>G	P	Korean	105 AERD, 125 NC, 111 ATA	2006	[15]
Aspirin	AERD	CysLTR2	Cysteinyl leukotriene receptor2	rare allele –819T>G, 2078C>T, 2534A>G	P	Korean	66 AERD, 134 ATA, 152 NC	2004	[16]
Cyclooxygenase, prostanoid gene and HLA-related markers									
Aspirin	AERD	PTGER	Prostanoid gene	T allele of PTGIR 1915T>C	P	Korean	108 AERD, 93 ATA, 140 NC	2007	[21]
Aspirin	AERD	COX2	Cyclooxygenase	C allele of –765G>C	P	Polish	112 AIA, 198 ATA	2004	[19*]
Aspirin	AERD	HLA	Human leukocyte antigen	DPB1*0301	P	Korean	76 AERD, 73 ATA, 91NC	2004	[23]
Aspirin	AERD	TBXA2R	Thromboxane receptor	C allele of +795T>C	P	Korean	93 AERD, 172 ATA, 118 NC	2005	[20]
Eosinophils-related gene									
Aspirin	AERD	CCR3	Chemokine receptor 3	G allele of –520T>G and –174C>T	P	Korean	191 AERD, 139 AICU, 217 NC	2009	[26]
Aspirin	AERD	CRTH2	Chemoattractant receptor	–466T of –466T>C	P	Korean	107AERD, 115ATA, 133NC	2009	[25]

AERD, aspirin exacerbated respiratory disease; AIA, aspirin-intolerant asthma; AICU, aspirin intolerant chronic urticaria; ATA, aspirin-tolerant asthma; ATCU, aspirin tolerant chronic urticaria; Y, positive association.

production in AERD patients. *TBXA2R* +795T>C and *TBXA2R* -4684T>C were shown to be associated with AERD in a Korean population [14,17]; however, this has not been replicated in other populations to date. Sixty-three candidate genes were investigated in a Japanese population [25] and a functional SNP of the PGE2 receptor subtype 2 (EP2) gene was associated with AERD by blocking the effects of PGE2 on inflammation. The *HLA DPB1**0301 allele was replicated as a marker for AERD [16] which was reported earlier in Polish population [26].

Eosinophil-related genes

Two genetic polymorphisms related to eosinophil activation were suggested by the findings of a study in a Korean population. The chemoattractant receptor molecule expressed in Th2 cells, the *CRTH2* -466T>C polymorphism, could increase serum and cellular eotaxin-2 production by lowering the *CRTH2* expression, leading to eosinophilic infiltration in AERD patients [19]. The chemokine CC motif receptor (CCR3) has been described as a key chemokine for eosinophil migration. The mutation rate of *CCR3* at -520 T>C was reported to be significantly higher in AERD patients in whom mRNA expression was significantly increased after ASA provocation [18].

Genetic studies of aspirin-intolerant chronic urticaria

The genes associated with leukotrienes and atopy

The C allele in the *LTC4* -444A>C promoter polymorphism was reported as a risk factor for AIU in a Venezuelan population (Table 2) [27–29,30*,31,32]. The frequency of the high-affinity IgE receptor *FCER1A* at the -344T was significantly higher in AICU patients than in control group [28], which was not replicated in a Polish population [33]. The genetic polymorphism at *FCER1G* -237G was significantly associated with atopic status and basophil histamine releasability in AICU patients [29].

Histamine-related genes

The histamine *N*-methyl transferase, *HNMT* 939A>C polymorphism was associated with the AICU phenotype by regulation of enzymatic activity and histamine release from peripheral basophils [30*]. No significant associations were found between the two histamine receptor genes *HRH1* and *HRH2* and the AIU phenotype in a Korean population [34].

Human leukocyte antigen and related cytokine genes

The *HLA-DRB1**1302 and *HLA-DB1**0609 alleles were suggested as potential genetic markers for both AIAU and AICU [32]; however, the findings were not replicated in Caucasian patients [35]. In another study, two promoter polymorphisms of TNF- α at -1031T>C and -863C>A were suggested to contribute to the development of AIU and AIAU, respectively [31].

Antibiotic hypersensitivity

The clinical manifestations of antibiotic allergy may be cutaneous, organ-specific, systemic, or various combinations of these findings [36–39,40*,41–51] (Table 3). The β -lactams including penicillin, cephalosporin, and carbapenem are the most common causative drugs followed by co-trimoxazole and quinolone. The major pathogenic mechanism associated with β -lactam antibiotics is IgE-mediated reaction enhanced by IL-4 and IL-13, which bind to the IL-4 receptor- α chain [52,53].

There have been several reports on the association of these SNPs and immediate hypersensitivity reactions to β -lactam antibiotics. The IL-4RA 50II, 478SS, 551QQ, and their haplotype ISQ have been associated with both higher total IgE levels and risk of β -lactam allergy in the Italian population [38]. Similarly, the IL-4RA 576Q allele

Table 2 Genetic and ethnic risk factors in aspirin intolerant urticaria

Drug	Phenotype	Gene	Full name	Genotype	Association	Population	Sample Size	Year	Reference
Genes related to leukotriene and atopy									
Aspirin	AIU	LTC4S	Leukotriene C4 synthase gene	C allele of A-444C	P	Venezuela	110 AIU, 165 control	2009	[27]
Aspirin	AICU	FCER1	High-affinity IgE receptor (FcepsilonR1)	T allele of FCER1A -344C>T	P	Korean	105 AICU, 154 ATCU, 222 NC	2007	[28]
Aspirin	AICU	FCER1	High-affinity IgE receptor (FcepsilonR1)	AG + GG of FCER1B E237G, and G allele of FCER1G -237T>G	P	Korean	119 AICU, 154 ATCU, 224 NC	2008	[29]
Histamine-related genes									
Aspirin	AICU	HNMT	Histamine <i>N</i> -methyltransferase	A allele of HNMT 939 A>G	P	Korean	111 AICU, 154 ATCU, 152 NC	2009	[30*]
HLA and related cytokines genes									
Aspirin	AIU	TNF- α	Tumour necrosis factor	T allele of TNF-1031T>C and C allele of TNF-863C>A	P	Korean	120 AICU, 119AIAU, 524 NC	2009	[31]
Aspirin	AIU	HLA	Human leucocyte antigen	DRB1*1302-DQB1*0609-DPB1*0201	P	Korean	94 AIU, 185NC	2005	[32]*

AICU, aspirin intolerant chronic urticaria; AIU, aspirin intolerant urticaria; NC, normal healthy control.

Table 3 Genetic and ethnic risk factors in antibiotics hypersensitivity

Drug	Phenotype	Genotype	Association	Population	Sample Size	Year	Reference
Immediate hypersensitivity reactions to β -lactams β -Lactams	Immediate hypersensitivity	IL-4RA I50V (I75V)	Y	Italian	P: 210/HC: 265	2006	[38]
			Y	French	P: 44/HC: 44	2006	[39]
			Y	Chinese	P: 242/HC: 220	2009	[40*]
			N	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[41]
		IL-4RA Q551R (Q576R)	Y	Chinese	P: 245/HC: 101	2005	[42]
			Y	Italian	P: 210/HC: 265	2006	[40*]
			Y	Chinese	P: 242/HC: 220	2009	[42]
			N	French	P: 44/HC: 44	2006	[43]
		IL-4RA S478P (S503P)	Y	Italian	P: 210/HC: 265	2006	[43]
			Y	Italian	P: 210/HC: 265	2006	[43]
		IL-13 -1055C>T/ -1111C>T combined with IL-4RA SNPs	Y				
			Y				
		IL-13 R130Q combined with IL-4RA SNPs	Y	Italian	P: 210/HC: 265	2006	[43]
			Y	Italian	P: 210/HC: 265	2006	[43]
		IL-13 R130Q	N	Chinese	P: 158/HC: 89	2005	[46]
		IL-4 rs2070874	Y	P: 22 W and 1 B C: 38 W and 1 B in the US	P: 23/HC: 39	2008	[44]
			Y	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
		KIF3A rs10062446	Y	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
		KIF3A rs11740584	Y	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
			Y	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
		IL-4 -589C>T	N	Chinese	P: 245/HC: 101	2005	[43]
		IL-4-IL-13-SNP3	Y	Chinese	P: 158/HC: 89	2005	[46]
		IL-4-IL-13-SNP4	Y	Chinese	P: 158/HC: 89	2005	[46]
		IL-10 -819C>T	Y	French	P: 44/HC: 44	2006	[43]
			N	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
		IL-10 -592C>A	Y	French	P: 44/HC: 44	2006	[43]
			N	P: 22 W and 1 B C: 38 W and 1 B In the US	P: 23/HC: 39	2008	[44]
		FCERIB E237G	Y	Chinese	P: 448/HC: 101	2004	[44]
			N	French	P: 44/HC: 44	2006	[43]
Hypersensitivity reactions to sulfamethoxazole (SMX) in HIV-infected patients SMX	Fever, rash	NAT2 slow acetylator genotypes [†]	N	W	P: 39/C: 46	1994	[45]
			N	French P: 94.6% W, 5.4% NW	P: 56/	2000	[46]
	Fever, rash, SJS, GI manifestations, neutropenia	CYP2C9*2,	N				
		CYP2C9*3,		C with (+) HIV: 93.2% W, 6.8% NW	C with (+) HIV: 89/		
		GSTP1b, GSTM1 null, GSTT1 null, NAT2 slow acetylator genotypes [†]		HC: W In the UK	HC: NA		
	Rash, fever, SJS	NAT2*4, 5A, 5B, 5C, 5F, 6A, 6E, 7A, and 7B	N	35 W, two African, two mixed, and one Asian in the UK	P: 32/	2003	[47]
			N		C with (+) HIV: 8/ HC: 26		
	Cutaneous reaction	CYP2C9*1*1 GSTP1*A/A	Y	French	P: 36/HC: 62	2005	[48]
			N	French	P: 36/HC: 62	2005	[57]
HLA and delayed hypersensitivity reactions Amino-penicillins Amoxicillin/clavulanic acid Flucloxacillin Others Antibiotics	Delayed hypersensitivity Jaundice Liver injury	HLA-A2, DRw52, DR4	Y	Italian	P: 24	1998	[49]
		HLA-DRB1*1501	Y	Scottish	P: 20/HC: 134	2000	[50]
		HLA-B*5701	Y	European	P 51/HC 282	2009	[5]
	Cutaneous reactions	CD40 -1C>T, CD40LG -3458A>G	Y	Korean	P: 200/HC: 185	2009	[51]
			Y	Korean	P: 200/HC: 185	2009	[51]

B, Black; C, controls; CYP, cytochrome P450; FCERIB, Fc ϵ receptor I β ; GI, gastrointestinal; GST, Glutathione S-transferase; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IL, interleukin; KIF3A, Kinesin family member 3A, gene in the same linkage disequilibrium block as IL-4; N, no; NA, not assessable; NAT, *N*-acetyl transferase; NC, normal controls; NW, non-White; P, patients; SJS, Stevens-Johnson syndrome; SMX, Sulfamethoxazole; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; W, White; Y, positive association.

[†] NAT2 282C>T, 481C>T, 590G>A, 857G>A.

was associated with immediate hypersensitivity reactions to penicillin and high specific IgE to penicillin, and the IL-4RA 75I allele was associated with penicillin-induced urticaria in a Chinese population [40*,43]. The IL-4RA I75V variant was associated with an immediate β -lactam allergic response in female French patients with atopy [39], which was not replicated in a US population [41]. The SNP of IL-13 R130Q at exon 4 was associated with high total IgE levels [54]. IL-13 130RQ + QQ and -1055/-1111C>T with predominant homozygous genotypes of the previously mentioned three SNPs of IL-4RA I50V, S478P, and Q551R were significantly associated with immediate hypersensitivity reactions to β -lactams in an Italian population [38] but not in a Chinese population [42].

IL-10 plays a pleiotropic role in immune regulation and inflammation [55]. Three SNPs in the IL-10 gene promoter, at -1082 G>A, -819 C>T, and -592 C>A may influence IL-10 production *in vitro* [56,57]. It has been reported that atopic women homozygous or heterozygous for the IL-10 -819T/-592A allele have a higher risk for developing an immediate IgE-dependent allergy to β -lactams in the French population [39] and that the allele was responsible for low expression of the cytokine [58]. The frequency of the -1082A allele was significantly higher in patients with specific IgE or IgG antibodies to penicillin compared with controls in a Chinese population. There has been a study suggesting a significant association between the FCER1B E237G SNP and high specific IgE antibodies to benzylpenicillin, phenoxymethylpenicillin, and ampicillin [44], which were not replicated in the French population [39].

Sulfamethoxazole (SMX) in combination with trimethoprim (cotrimoxazole) is the drug of choice for treatment of *Pneumocystis carinii* pneumonia in HIV-positive patients [49]. The main routes of SMX metabolism are acetylation, glucuronidation, *N*-hydroxylation, and 5-hydroxylation [59]. Several studies in diverse populations have shown no association of NAT2, CYP2C9*2, CYP2C9*3, glutathione *S*-transferase (GST) M1, GSTT1, and GSTP1 with SMX allergy [45–47], with the exception of the GSTP1 SNP in a French population [48].

The higher prevalence of HLA-A2 and DRw52 and lower prevalence of DR4 were associated with delayed hypersensitivity reactions to penicillin in an Italian population [60]. The HLA-DRB1*1501 allele was a risk factor for jaundice induced by amoxicillin/clavulanic acid in a Scottish population [50]. Recently, using genome-wide and candidate gene approaches, HLA-B*5701 has been identified as a major determinant of drug-induced liver injury due to flucloxacillin in a European population [5].

The genetic interaction between CD40 and the CD40 ligand might favor the development of cutaneous allergic reactions to all types of antibiotics including penicillin, cephalosporin, and quinolone in a Korean population [51].

Adverse reactions associated with antituberculosis drugs

The most frequent adverse reactions of antituberculosis (anti-TB) drug are hepatitis, skin reactions, gastrointestinal disorders, and neurological disorders, of which hepatitis is the most serious. Older age, female sex, malnutrition, a slow acetylator status, HIV infection, underlying liver disease, high alcohol intake, and hepatitis B or C virus infections have been suggested as risk factors [61–63,64*,65–67]. The slow acetylator status, which can be determined genetically, can be useful for determining phenotypic and/or genotypic factors, indicating that anti-TB drug-induced hepatitis is likely to result from the interaction between environmental and genetic factors that determine drug disposition and metabolism.

Although the exact mechanism of anti-TB drug-induced hepatitis is unknown, the enzymes involved in drug metabolism have significant effects on the synthesis and detoxification of reactive toxic metabolites [68]. Therefore, most genetic studies have focused on a few enzymes involved in metabolism including the cytochrome P450 (CYP450) enzymes [69–73,74*], the hepatic enzyme *N*-acetyltransferase 2 (NAT2) [72,74*,75–81], GST [82,83], and manganese superoxide dismutase (MnSOD) [84] (Table 4). The CYP2E1c1/c1 genotype has been found to be a genetic risk factor by increasing CYP2E1 activity and the production of hepatotoxic metabolites of these drugs [70]. There was no association of the CYP2E1 genetic polymorphism in Korean and British populations [69,72].

The NAT2 genetic polymorphism that affects changes in the acetylation phenotype may contribute to the risk of anti-TB drug-induced hepatitis. Among 27 known alleles of the NAT2 gene, the slow acetylator variants including NAT2*5, NAT2*6, and NAT2*7 have been significantly associated with the risk of hepatitis. However, the allele frequencies of these variants have shown ethnic differences [81]. For Asian patients, the NAT2*5 allele is rare and NAT2*6 is the predominant one with low acetylation activity. For Caucasians, the NAT2*7 allele is rare and NAT2*5 is the dominant one. Genetic association results have also varied (Table 4) in different ethnic groups. Slow acetylator variants have shown more significant associations in the Asian population but not in the British. Moreover, an additive effect from two genetic polymorphisms of CYP2E1 and NAT2 has also been

Table 4 Genetic factors associated with antituberculosis drug-induced hepatitis

Drug	Gene		Genotype	Assoc.	Population	Year	Reference
INH	CYP2E1	Cytochrome P450 2E1	*C/*C	Y	Chinese	2009	[73]
INH			*C/*C	N	British	2009	[72]
INH			*C/*C	N	Korean	2007	[69]
INH			*C/*C	Y	Taiwanese	2003	[70]
INH			*1A/*1A genotype	Y	Mixed population	2006	[71]
INH			p1055C/T,p352A/G, p333A/T	N	Korean	2009	[74 [•]]
INH	NAT2	N-acetyltransferase 2	Slow activator variants	N	British	2009	[69]
INH			Slow activator variants	Y	Korean	2007	[71]
INH			Slow activator variants	N	Mixed population	2006	[71]
INH + RMP			Slow activator variants	Y	Japanese	2003	[76]
INH			Slow activator variants	Y	Taiwanese	2002	[75]
INH			p9796T>A, R197Q	Y	Korean	2009	[74 [•]]
INH + RMP	GST	Glutathione S-transferase	GST M1/M1	N	Caucasian	2008	[84]
anti-TB drugs			GST M1/M1	Y	Taiwanese	2007	[84]
INH + RMP			GST T1/T1	Y	Caucasian	2008	[83]
anti-TB drugs	MnSOD	Manganese superoxide dismutase	T/C or C/C	Y	Taiwanese	2007	[84]
anti-TB drugs	HLA	Human leukocyte antigen	DRB1*0701-DQA1*0201-DQB1*0201	Y	India	2002	[85]

INH, isoniazid; RMP, rifampicin; Y, positive association.

reported [72]. When the CYP2E1c1/c1 genotype was combined with the slow acetylator genotype of NAT2, the odds ratio (OR) increased from 2.52 to 7.43 [72].

Increased oxidative stress or reduced glutathione may contribute to anti-TB drug-induced hepatitis. The MnSOD variant C allele and GSTM1 null genotype may be related to anti-TB drug-induced hepatitis [84]. The variation in the association of GST gene polymorphism in different ethnic groups was also found in the Spanish population; the GST T1/T1 genotype was significantly associated with anti-TB drug-induced hepatitis instead of the GST M1/M1 genotype [83]. The other drug-metabolizing enzymes including *CYP2C9*, *CYP2C19*, *CYP2D6*, *UGT1A1*, and *UGT1A3* have also been investigated in a Korean population; however, no significant association was found [74[•]].

Furthermore, immunological factors such as highly polymorphic human leukocyte antigen (HLA) molecules may contribute to anti-TB drug-induced hepatitis. The HLA molecule allele, DRB1*0701–DQA1*0201–DQB1*0201 haplotype was found to be associated with hepatitis in an Indian population [85].

Anti-TB drug-induced hepatitis can be fatal when not recognized and treated properly. Therefore, identification of the genetic factors for each drug is needed for early diagnosis and prevention. Further investigations are needed to better understand the genetic polymorphisms of enzymes involved in metabolism and the production of toxic metabolites associated with anti-TB drugs.

isms of enzymes involved in metabolism and the production of toxic metabolites associated with anti-TB drugs.

Severe drug hypersensitivity

The hypersensitivity syndrome (HSS) including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is characterized by systemic manifestations with multiorgan involvement and a high risk of mortality, in addition to skin rashes. Several novel genetic factors for severe drug hypersensitivity (SDH) have been identified. The genetic predisposition to the phenotypic manifestations is specific to drug and ethnic groups. Although the common offending drugs may be different with regard to geographic distribution and ethnicity, NSAIDs, carbamazepine (CBZ), allopurinol, and, recently, abacavir are usually ranked among the most common causes.

Carbamazepine hypersensitivity

The most significant genetic association has been detected in a Han Chinese cohort in Taiwan, where a 100% prevalence of the HLA-B*1502 allele among 44 patients with CBZ-induced SJS was identified, compared with a frequency of 3% among 101 CBZ-tolerant patients [OR 2504, 95% confidence interval (CI) 126–49522] [86–88] (Table 5). These findings were further confirmed by an extended cohort of ethnic Chinese living in Europe [89], and Hong Kong [90], and in other Asian populations

Table 5 Genetic factors associated with carbamazepine-induced severe cutaneous adverse reactions (SCARs)

Drug	Phenotype	Gene	Genotype	Association	Population	Sample size	Year	Reference
Carbamazepine	SJS	HLA						
	SJS/TEN	HLA-B	*1502	Y	Indian	8P	2009	[92]
		HLA-B	*1502	N	Korean	10P, 50C	2009	[95]
			*3101	Y (OR 6.1)				
	MPE	HLA-B	*1502	N	Thai		2008	[91]
	SJS/TEN	HLA-B	*1502	N	Japanese	7P	2008	[94]
	SJS/TEN	HLA-B	*1502	Y (OR 25.5)	Thai	6P	2008	[91]
	MPE	HLA-B	*1502	N	Han Chinese in HK		2007	[90]
	SJS/TEN	HLA-B	*1502	Y (OR 71.9)	Han Chinese in HK	4P	2007	[90]
	HSS/MPE	HLA-B	*1502	N	Caucasian (W, UK)	56P, 43C	2006	[93]
		HLA-B	*0702	Protection				
	SJS/TEN	HLA-B	*1502	Y (OR 1357–2504)	Han Chinese in Taiwan	60P	2006	[86,88]
Lamotrigine	SJS/TEN	HLA-B	*1502	N in Whites, Y in Asian	Germany and France; Vietnam, China, Cambodia and Reunion Island	12P	2006	[89]
	HSS/MPE	HLA-B	*1502	Y	Han Chinese in Taiwan		2006	[88]
	SCAR	HLA-B	*5802	Y	Caucasian (W, EU)	65P, 43C	2009	[96]
		HLA-A	*6801	Y				
		HLA-Cw	*0718	Y				
Carbamazepine		HLA-DQB1	*0609	Y				
		HLA-DRB1	*1301	Y				
	HSS/MPE	HSP70 gene cluster	HSP1A + 1911C/G	Protection	Caucasian (W, UK)	61P, 44C	2006	[97]
	HSS/MPE	TNF	HSP1A + 438C/T HSPA1L+ 2437T/C TNF-DR3-DQ2 haplotypes	Protection Protection Y (OR 3.2)	Caucasian (W, UK)		2006	[93]

B, black; C, controls; H, Hispanic; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; N, no association; P, patients; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; W, white population; Y, positive association.

including Thai [91] and Indian [92] groups. Since these recent reports on the very strong association between HLA-B*1502 and CBZ-induced SJS/TEN in the Han Chinese, the US FDA approved revision of the labels of products containing CBZ. The revised labels clearly state that patients with Chinese ancestry should be screened for the HLA-B*1502 allele before starting

CBZ treatment and that HLA-B*1502-positive patients should avoid CBZ. By contrast, absence of an association between HLA-B*1502 and CBZ-induced SJS/TEN has been reported in a Caucasian population [93] as well as other Asian patients such as Japanese [94] and Koreans [95]. The risk of disease associated with a genetic polymorphism is influenced by its prevalence. The

Table 6 Genetic factors associated with abacavir-induced severe cutaneous adverse reactions (SCARs)

Phenotype	Gene	Genotype	Association	Region	Population	N	Year	Reference
HSS	HLA							
HSS	HLA-B	*5701	N (0/534P)	Korea	100% Korean	4P, 93C	2009	[105]
HSS	HLA-B	*5701	Y	19 countries	83% W, 12% B, 5% others	1965	2008	[101]
HSS	HLA-B	*5701	Y	Western Australia HIV Cohort	75% W, 9% Aboriginal, 6% African, 10% Asia	260	2006	[102]
HSS	HLA-B	*5701	Y (OR 7.9)	UK	Caucasians	63	2004	[104]
HSS	HLA-B	*5701	Y	Western Australia HIV Cohort	86% Europe, 14% others	248	2004	[103]
HSS	HSP70	Homo variant	Y					
HSS	HLA-B	*5701	Y in W&H N in B	USA	66% W, 19% H, 15% B	531	2004	[103]
HSS	HLA-B	*5701	Y	Western Australia HIV Cohort	89% W	185	2002	[100]
HSS	HLA-DR7		Y					
HSS	HLA-DQ3		Y					
HSS	HLA-B	*5701	Y	USA	74% W, 14% B, 11% H, 2% Others	200	2002	[99]

B, black; C, exposed controls; H, Hispanic; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; N, no association; P, patients; W, white population; Y, positive association.

Table 7 Genetic factors associated with allopurinol-induced severe cutaneous adverse reactions (SCARs)

Phenotype	Gene	Genotype	Association	Population	N	Year	Reference
	HLA						
SJS/TEN	HLA-B	*5801	Y (OR 348.3)	Thai	27P, 54C	2009	[111]
SJS/TEN/DRESS	HLA-B	*5801	Y (OR 59.5)	Korean	16P, 57C	2009	[112]
SJS/TEN	HLA-B	*5801	Y	Japanese	58P (CBZ, Allo)	2008	[94]
SJS/TEN/DRESS	HLA-B	*5801	Y	Singapore	51P	2008	[109]
HSS/SJS/TEN	HLA-B	*5801	Y (OR 580.3)	Han Chinese in Taiwan	51P, 135C, 93H	2005	[108]
	HLA-A	*3303	Y (OR 9.3)				
	HLA-Cw	*0302	Y (OR 97.7)				
	HLADRB1	*0301	Y (OR 12.7)				

Allo, allopurinol; C, exposed controls; CBZ, carbamazepine; DRESS, drug rash with eosinophilia and systemic symptoms; H, healthy controls; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; P, patients; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Y, positive association.

frequency of HLA-B*1502 is highest (10–15%) among Asian groups from certain parts of China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan. South Asians, including Indians, are at moderate risk (2–4%), whereas patients with Japanese or Korean ancestry are at low risk (<1%) [98]. In countries with mainly Caucasian populations, the overall rate of CBZ-related SJS/TEN is very low, estimated to be one to six per 10 000 newly exposed patients. Ethnicity appears to play an important role in the association. In some Asian populations, HLA-B*1502 was also detected in patients with other medications used for epilepsy such as lamotrigine and phenytoin [90]. However, in a recent case-control study [96] of persons of European origin, suggestive evidence was obtained only for B*5801, A*6801, Cw*0718, DQB1*0609, and DRB1*1301, whereas none of the cases carried B*1502 among 22 patients with lamotrigine-induced severe cutaneous adverse reactions. Alfirevic *et al.* [93,97] reported a potential protective role of HLA-B*0702 and three SNPs of the HSP-70 gene cluster in Caucasian patients with CBZ-induced severe cutaneous adverse reactions (SCAR).

Abacavir hypersensitivity

A strong positive correlation between HLA-B*5701 and abacavir hypersensitivity reactions was reported by two independent research groups [99–102] (Table 6). Subsequent studies have shown that the combination of the HLA B*5701 allele and a polymorphism for the heat shock protein-Hom (HSP1AL) has a greater predictive accuracy than HLA B*5701 itself [103]. This association has been replicated in Caucasian and Hispanic ethnic groups, in cohorts of patients from both the UK and USA [104,106]. However, the ORs in these studies were lower than those obtained by Mallal *et al.* [100]. Furthermore, the same association has not been replicated in the black [104], or Korean populations [105]. Nevertheless, the association of HLA-B*5701 with abacavir-induced HSS in Caucasians has been confirmed in prospective multinational cohort studies

[107]. These studies have also demonstrated that the overall rates of abacavir [90] discontinuation were reduced when the HLA-B*5701 status was incorporated into clinical decision-making, indicating that the cost-effectiveness of genetic screening was associated with the prevention of serious abacavir hypersensitivity with HLA-B*5701.

Allopurinol hypersensitivity

The association of HLA-B*5801 with allopurinol-induced SCARs detected in the Han Chinese in Taiwan [108] has been replicated not only in Asian populations including the Chinese [109], Japanese [94,110], Thai [111], and Koreans [112] but also in Caucasians [89] (Table 7). Although the statistical association was higher for the Han Chinese (OR 580.3) than for the European data (OR 80), the HLA-B*5801 allele, in contrast to HLA-B*1502 and HLA-B*5701, was found to be more evenly distributed among different ethnic groups (Table 3).

Without stratification of the offending drugs, Ueta *et al.* [113] reported that HLA-A*0206 was associated with SJS/TEN with ocular complications in Japanese patients.

Conclusion

Identification of genetic risk factors responsible for drug hypersensitivity is an important focus for future tasks. Generally, the candidate genes studied with regard to drug hypersensitivity are limited to genes coding drug targets, transporters, and the enzymes involved in drug metabolism. The traditional candidate gene approach is limited and a more extensive genome wide approach is needed to investigate the genetic basis of drug hypersensitivity with well characterized study participants and large populations. Such genetic markers can be used for testing and prevention and reduce the morbidity and mortality associated with drug hypersensitivity reactions.

References and recommended reading

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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