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PHARMACOGENETICS

Pharmacogenetics of hypersensitivity drug reactions

Simone Negrini[a,*], **Laurent Becquemont**[b]

[a] *Department of internal medicine, clinical immunology unit, centre of excellence for biomedical research, university of Genoa, 16132 Genoa, Italy*
[b] *Pharmacology department, faculty of medicine Paris-Sud, UMR 1184, CEA, DSV/iMETI, division of immuno-virology, IDMIT, Inserm center for immunology of viral infections and autoimmune diseases, hôpital Bicêtre, university Paris Sud, Assistance publique—Hôpitaux de Paris, 94275 Le Kremlin-Bicêtre, France*

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Summary Adverse drug reactions are a significant cause of morbidity and mortality and represent a major burden on the healthcare system. Some of those reactions are immunologically mediated (hypersensitivity reactions) and can be clinically subdivided into two categories: immediate reactions (IgE-related) and delayed reactions (T-cell-mediated). Delayed hypersensitivity reactions include both systemic syndromes and organ-specific toxicities and can be triggered by a wide range of chemically diverse drugs. Recent studies have demonstrated a strong genetic association between human leukocyte antigen alleles and susceptibility to delayed drug hypersensitivity. Most notable examples include human leukocyte antigen (HLA)-B*57:01 allele and abacavir hypersensitivity syndrome or HLA-B*15:02 and HLA-B*58:01 alleles related to severe cutaneous reactions induced by carbamazepine and allopurinol, respectively. This review aims to explore our current understanding in the field of pharmacogenomics of HLA-associated drug hypersensitivities and its translation into clinical practice for predicting adverse drug reactions.

Abbreviations

ADRs	adverse drug reactions
APC	antigen-presenting cell
DIHS	drug-induced hypersensitivity syndrome
EMA	European Medicines Agency
FDA	Food and Drug Administration
HDRs	hypersensitivity drug reactions
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
MPE	maculopapular eruption
NPV	negative predictive value
PPV	positive predictive value
SJS	Stevens-Johnson syndrome
TCR	T-cell receptor

* Corresponding author. Department of internal medicine, university of Genoa, viale Benedetto XV, 6, 16132 Genoa, Italy.
E-mail address: negrini@unige.it (S. Negrini).

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TEN toxic epidermal necrolysis
WHO World Health Organization

Hypersensitivity drug reactions

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as an ''unintended, noxious response to a drug that occurs at a dose usually prescribed for human patients'' [1]. ADRs are recognized as a major health problem, in the United States they are responsible of 6—7% of hospitalization cases and represent the fourth to sixth leading cause of death accounting for 100,000 fatal cases annually [2]. In Europe, it is estimated that 5% of all hospital admission and 197,000 deaths per year are caused by ADRs [3]. Along with the mortality and morbidity burden, it is estimated that the total cost to society of ADRs is $ 177 billion and € 79 billion in the USA and Europe, respectively [3,4]. Moreover, ADRs remain a huge cost burden for pharmaceutical industry representing the main cause of drug withdrawal from the market [5].

The historical pharmacologic classification of ADRs by Rawlins and Thompson classifies these into two main categories [6]. Type A reactions are predictable, dose-dependent, and related to pharmacologic properties of the drug, and Type B reactions, accounting for approximately 10% of all ADRs, are unpredictable, not dose-dependent and correspond to hypersensitivity drug reactions (HDRs). Occurring only in susceptible individuals Type B ADRs are sometimes termed ''idiosyncratic''. Since, terminology used to define HDRs is often confusing due to a lack of commonly accepted definitions, the European Academy of Allergology and Clinical Immunology published a statement paper in order to standardize the nomenclature of allergic diseases, also including drug allergy [7]. The revised nomenclature has been further adopted by the World Allergy Organization [8]. The proposed classification define as ''drug allergy'' those HDRs in which immunologic mechanisms may be demonstrated, while HDRs with symptoms and signs similar to real allergies but not triggered by a specific immunological mechanism are referred to as ''non-allergic drug hypersensitivity'' (e.g. non-specific histamine release, arachidonic acid pathway activation, bradykinin pathway alteration, etc.). With regard to the onset of symptoms, drug allergies may be further classified as immediate or delayed, suggesting also the immunological mechanism underlying the reaction [7,8].

Immunological basis of hypersensitivity drug reactions

Immediate reactions occur immediately after drug exposure, are IgE-dependent, and derive from mast cell degranulation and release of pro-inflammatory mediators. Clinical manifestations include erythema, urticaria, angioedema, bronchospasm, and anaphylactic shock. Delayed hypersensitivity reactions generally occur days, or even weeks, after drug exposure and are mediated by antigen-specific T lymphocytes. Examples of delayed-type HDRs include both systemic syndromes (e.g. drug rash with eosinophilia and systemic symptoms) and organ-specific toxicities (e.g. hepatitis, pneumonitis, etc.). Delayed-type hypersensitivity reactions correspond to type IV hypersensitivity according to the classification system of Gell and Coombs [9]. Since T-cells can orchestrate different immune responses resulting in different clinical entities, delayed reactions can be further classified into IVa (Th1 cells), IVb (Th2 cells), IVc (cytotoxic T-cell), and IVd (neutrophils) [10].

Since drugs are generally too small to stimulate an immune response (molecular weights < 1000 Daltons), several, non-mutually exclusive, models have been proposed to explain how drugs can become immunogenic and trigger T-cells: the ''hapten/pro-hapten model'', the ''Pi (pharmacologic interaction with immune receptors) concept'', the ''altered peptide repertoire hypothesis'' and the ''danger signal'' theory. The ''hapten/pro-hapten model'' proposes that a chemically reactive drug, acting as hapten, can bind covalently to self-proteins (carriers) creating fully antigenic complexes. These neo-antigens are processed by an antigen-presenting cell (APC), loaded onto the HLA molecules and then presented to appropriate T-cells. The pro-hapten is a chemically non-reactive drug that becomes reactive upon metabolism [11]. According to ''pi-concept hypothesis'', a chemically inert drug, unable to covalently bind to proteins, is able to structurally ''fit'' into the T-cell receptor. This interaction needs neither metabolism nor antigen processing. The initial stimulation of the T-cell receptor (TCR) is further supplemented by TCR-HLA interaction and probably must take place in a context of hyper-reactive T-cells with a low threshold level of activation [12—14]. The ''altered peptide repertoire hypothesis'' proposes that the drug binds the antigen-binding groove of HLA thus modifying the antigen-binding cleft thus altering the repertoire of self-peptides that are bound and presented. Since T-cells are educated to be tolerant to a specific pool of peptides during thymic maturation, the presentation of these neo-self-peptides may induce T-cell activation. Recent observations provide strong evidence that this model is implicated in HDRs related to abacavir and carbamazepine [15]. Last hypothesis proposes that the drug itself or concomitant situations (e.g. viral infections) can provide ''danger signals'' capable of upregulating costimulatory molecules and cytokines in innate immune cells, thus facilitating the immune activation [11].

The human leukocyte antigen (HLA) molecules plays a crucial role in T-cells activation by presenting processed antigens to the T-cell receptor expressed on T lymphocytes. Broadly speaking, there are two main types of HLA molecules: the HLA class I molecules, expressed on most nucleated cells, and the HLA class II molecules, expressed by APCs, such as monocytes or dendritic cells. HLA class I molecules are encoded by three loci known as HLA-A, HLA-B, and HLA-C; HLA class II molecules are encoded by three loci known as HLA-DR, HLA-DQ, and HLA-DP. HLA class I and class II molecules initiate the adaptive immune response by presenting antigens to CD8+ (cytotoxic) and CD4+ (helper) T-cells. Because the HLA molecules need to present an huge variety of ''self'' and ''non-self'' peptides, the HLA genes are both numerous and extremely polymorphic. Taking into account the crucial role of HLA in immune response it is not surprising that particular HLA alleles have been associated with susceptibility to diseases in which the immune system is considered the principal mediator, like infectious or autoimmune disorders [16,17]. In the same way, certain HLA alleles

have been associated with an increased risk of delayed HDRs. The evidence that certain HLA alleles may increase the risk of HDRs has prompted the development of screening test strategies and labeling changes to drug information sheets.

To date, the best-characterized HLA-HDRs associations include abacavir, carbamazepine, and allopurinol.

Specific examples of HLA-related hypersensitivity drug reactions

Abacavir

Abacavir is a nucleoside analog reverse-transcriptase inhibitor used as part of combination therapy for the treatment of human immunodeficiency virus (HIV) infection. Abacavir is generally well tolerated, but 5—8% of patients may develop an hypersensitivity reaction generally within the first 6 weeks of treatment [18]. Abacavir hypersensitivity reaction is clinically characterized by fever, rash, constitutional, gastrointestinal and respiratory symptoms. Symptoms worsen with the continuation of abacavir and can be life-threatening if the drug is re-administered after discontinuation [19]. Even if Abacavir hypersensitivity was reported in the pre-marketing phase of its development, only in 2002, two independent groups described a strong association between the HLA-B*57:01 allele and susceptibility to develop abacavir hypersensitivity syndrome [20,21].

This association was successively reported by different groups [22—25], but it was definitively confirmed in 2008 with the results of the largest randomized clinical trial performed to date in pharmacogenetics: the PREDICT-1 trial. In this study, 1956 patients from 19 countries were randomized to either HLA-B*5701 genetic screening (carriers of HLA-B*5701 did not receive abacavir) or to the standard of care (no screening and all patients received abacavir). Genetic screening virtually eliminated all immunologically confirmed HDRs (0% in the screened group versus 2.7% in the control group), thus supporting a great translational potential of HLA-B*57:01 as screening test for abacavir-related HDR [26]. Nevertheless, the generalisability of the PREDICT-1 results to all races was limited by its prevalent Caucasian population (84% of the enrolled patients were Caucasian). The SHAPE trial, a case-control study including similar percentages of black and white patients, revealed a 100% negative predictive value (NPV) of HLA-B*57:01 testing for abacavir hypersensitivity both for black and white patients, thus confirming the value of the screening across different ethnicities [27]. A recent meta-analysis further confirmed that HLA-B*57:01 carriage is significantly associated with abacavir-induced hypersensitivity reactions in Whites, Blacks, and Hispanics [28]. The NPV of HLA-B*57:01 screening is 100% (which means that HLA-B*57:01 negative individuals will not develop hypersensitivity) making this test highly valuable in predicting the risk of abacavir-related HDR. Nevertheless, the positive predictive value (PPV) of HLA-B*57:01 genetic testing is estimated to be around 50% implying that around half of all patients found positive at screening actually will develop the HDR if exposed to abacavir. High NPV and low PPV seems to be a characteristic feature of HLA screening tests (Table 1) [29—33] suggesting that these markers are necessary but not sufficient for ADR onset, and other genes and/or environmental factors should be involved.

Interestingly, HLA-B*57:01 has also been associated to an increased risk of drug-induced liver injury in patients treated with the antibiotic flucloxacillin [34]. The association of HLA-B*57:01 with both abacavir hypersensitivity and flucloxacillin-induced hepatotoxicity indicates that the same HLA allele lead to completely different reactions triggered by chemically unrelated drugs. In addition, HLA-B*57:01 has been associated with slow or non-progression of HIV infection [35—37]. Taken together, these data seem to suggest that HLA-B*57:01 is related with an ''hyperactive'' immune response that, on one hand may increase the risk to develop hypersensitivity reactions, but, on the other hand, confer resistance to infections.

In light of the large number of evidences correlating HLA-B*57:01 and abacavir-induced HDR, the genetic screening prior to abacavir treatment is recommended by Food and Drug Administration (FDA), European Medicines Agency (EMA), and virtually all international HIV treatment guidelines [32,33]. Currently, HLA-B*57:01 is one of most, if not the most, commonly used pharmacogenetic marker in clinical practice.

Carbamazepine

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, also known as Lyell's syndrome) are severe mucocutaneous reactions characterized by extensive detachment of the skin. These skin reactions are considered to be variants of the same disease and they are classified according to the degree of skin involvement which is < 10% in SJS, and > 30% in TEN. A skin detachment of 10 to 30% of body surface area is named SJS/TEN overlap [38]. SJS/TEN are rare diseases with an incidence of 2—6 cases/million per year but both are associated with high morbidity and mortality (5% and 50% mortality for SJS for TEN, respectively) [38,39]. From a pathophysiological points of view, SJS/TEN are attributable to autoreactive CD8+ cytotoxic lymphocytes that cause keratinocytes death through the release of cytotoxic molecules, such as soluble-FasL, granzyme B, perforin, granulysin and pro-apoptotic cytokines [40]. In the vast majority of cases SJS/TEN are triggered by drugs and several medications are considered at high risk of inducing SJS/TEN [41].

Carbamazepine is an aromatic amine anticonvulsant widely employed to treat epilepsy, bipolar disorder, and trigeminal neuralgia. Carbamazepine is generally safe, but has been associated with maculopapular eruption (MPE), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (also known as DIHS [drug-induced hypersensitivity syndrome]), and more rarely SJS/TEN [42]. In 2004, Chung et al. reported a very strong association between carbamazepine-induced SJS/TEN and the HLA-B*15:02 allele in Han Chinese patients from Taiwan. They observed that all patients with carbamazepine-induced SJS/TEN carried the HLA-B*15:02 allele as compared to only 3% of drug-tolerant subjects and 8.6% of the general population [43]. Further studies have replicated this association in different Asian areas including China, Thailand, Malaysia, India, Vietnam, and Cambodia [44—53], and three recent meta-

Table 1 Most relevant genotype-based pharmacogenomics relationships between HLA and drug hypersensitivity [29—33].

Drug	Level of evidence [29]	Allele	Clinical manifestation	Population	Risk of ADR	Clinical implementation [29,32,33] French National Pharmacogenetics network (RNPGx) recommendations
Abacavir	1A	HLA-B*57:01	DRESS	Mixed population	Increased	FDA: boxed warning, test recommended, EMA: test required, PMDA: label information, HCSC: test recommended, CPIC: alternative drug for positive patients, test recommended DPWG: alternative drug for positive patients, virtually all HIV Treatment Guidelines: test required/recommended PPV = 55%, NPV = 100% for patch test confirmed, NNT to prevent ''1'' = 32 RNPGx reco: essential
Acetazolamide	4	HLA-B*59:01	SJS/TEN	Asian (Korean)	Increased	RNPGx recommendation: no indication in routine care
Acetaminophen	3	HLA-DQB1*02:02	SJS/TEN	Caucasian (Italian)	Increased	RNPGx reco: no indication in routine care
Allopurinol	1A	HLA-B*58:01	SJS/TEN	Mixed Population	Increased	European national competent authorities: warning (no genotyping recommendations), ACR: alternative drug for HLA-B*58:01 positive patients, CPIC: alternative drug for HLA-B*58:01 positive patients HLA-B*58:01 test PPV = 3%, NPV = 100% in Han Chinese, NNT to prevent ''1'' = 250 RNPGx reco: HLA-B*58:01 potentially useful namely in Asian ancestry populations (Han Chinese, Thaï and Taiwanese)
	2B	HLA-A*33:03	Drug Hypersensitivity, SJS/TEN	Mixed population	Increased	
	3	HLA-A*02:01	SJS/TEN	Asian	Decreased	
	3	HLA-B*48:01	Drug Hypersensitivity	Asian	Increased (not in all studies)	
	3	HLA-C*03:02	Rash	Asian (Korean)	Increased	
	3	HLA-C*08:01	Drug Hypersensitivity	Mixed population	Increased (not in all studies)	
	3	HLA-DQB1*05:02	SJS/TEN	Caucasian (Italian)	Increased	
	3	HLA-DR9; HLA-DR14	MPE	Asian	Increased	
	3	HLA-DRB1*03:01 (in LD with HLA-B*58:01 in some populations)	SJS/TEN	Asian (Han Chinese)	Increased	
	3	HLA-DRB1*15:02, HLA-DRB1*13:02	SJS/TEN	Caucasian (Italian)	Increased	
Aspirin	2B	HLA-DPB1*03:01	Asthma	Mixed population	Increased	N/A
	3	HLA-DPB1*04:01	Asthma	Mixed population	Decreased	RNPGx reco: HLA-B*58:01: no indication in routine care

Table 1 (*Continued*)

Drug	Level of evidence [29]	Allele	Clinical manifestation	Population	Risk of ADR	Clinical implementation [29,32,33] French National Pharmacogenetics network (RNPGx) recommendations
Azathioprine (or mercaptopurine)	3	HLA-DQA1*02:01, HLA-DRB1*07:01	Pancreatitis	European	Increased	N/A RNPGx reco: no indication in routine care
Carbamazepine	1A	HLA-B*15:02	SJS/TEN	Mainly Asian[a]	Increased	HLA-B*15:02 FDA: Boxed Warning, test required (patients with Asian ancestry), European national competent authorities: warning, test recommended (patients with Asian ancestry), PMDA: label information, HCSC: test recommended, CPNDS: drug contraindicated for positive patients Asian: PPV = 1.8%, NPV = 100%, NNT to prevent ''1'' = 461
	2A	HLA-B*15:11	SJS/TEN	Asian (Japanese, Korean, Han Chinese)	Increased	
	2B	HLA-A*31:01	DRESS, MPE, SJS/TEN	Mixed population[a]	Increased	
	2B	HLA-B*40:01	SJS/TEN	Asian (Han Chinese, Taiwanese)	Decreased	HLA-A*31:01 FDA: warning (no genotyping recommendations), European national competent authorities: warning (no genotyping recommendations), HCSC: test recommended, CPNDS: drug contraindicated positive patients Japanese: PPV = 12%, NPV = 99%, NNT to prevent ''1'' = 67 Caucasian: PPV = 43%, NPV = 92%, NNT to prevent ''1'' = 47 RNPGx reco: HLA-B*15:02 advisable in Asian ancestry populations (Han Chinese and Taiwanese)
	2B	HLA-C*03:02 (in LD with HLA-B*58:01 in some populations)	SJS/TEN	Mixed population	Increased	
	3	HLA-B*15:18	SJS/TEN	Asian (Japanese)	Increased	
	3	HLA-B*58:01	MEP	Asian (Han Chinese)	Decreased	
	3	HLA-B*58:01	SJS/TEN	Asian (Han Chinese)	Increased (decreased in one study)	
	3	HLA-B*59:01	SJS/TEN	Asian (Japanese)	Increased	
	3	HLA-B*13:01	Drug Hypersensitivity	Caucasian, Asian	Increased (not in all studies)	
	3	HLA-B*46:01	SJS/TEN	Asian	Decreased	
	3	HLA-DRB1*03:01	MEP	Asian (Han Chinese)	Increased	
Clozapine	3	HLA-DRB3*02:02	Agranulocytosis	Caucasian	Increased	N/A RNPGx reco: no indication in routine care
Dapsone	2A	HLA-B*13:01	Drug hypersensitivity	Asian	Increased	PPV = 7.8%, NPV = 99.8% NNT to prevent ''1'' = 84 RNPGx reco: no indication in routine care
	3	HLA-A*02:01	Drug hypersensitivity	Asian (Japanese, Korean, Chinese)	Increased (decreased in one study)	N/A RNPGx reco: no indication in routine care

Table 1 (*Continued*)

Drug	Level of evidence [29]	Allele	Clinical manifestation	Population	Risk of ADR	Clinical implementation [29,32,33] French National Pharmacogenetics network (RNPGx) recommendations
Flucloxacillin	3	HLA-B*57:01	Drug-induced liver injury	Caucasian	Increased	PPV = 0.12%, NPV = 99.99% NNT to prevent ''1'' = 13,819 RNPGx reco: no indication in routine care
Lamotrigine	3	HLA-B*58:01	SJS/TEN	Mixed population	Increased	N/A RNPGx reco: no indication in routine care
	3	HLA-B*15:02	SJS/TEN	Asian	Increased (only found in meta-analyses)	
Lapatinib	2B	HLA-DQA1*02:01	Drug-induced liver injury	Mixed population	Increased	HLA-DQA1*02:01 or HLA-DRB1*07:01 alleles carrier = FDA: warning (no genotyping recommendations), EMA: warning (no genotyping recommendations), HCSC: warning (no genotyping recommendations) RNPGx reco: potentially usefull
	3	HLA-DRB1*07:01	Drug-induced liver injury	Mixed population	Increased	
Methazolamide	2A	HLA-B*59:01	SJS/TEN	Asian (Korean, Japanese, Chinese)	Increased	N/A RNPGx reco: no indication in routine care
	2B	HLA-C*01:02	SJS/TEN	Asian (Korean, Chinese)	Increased	
Nevirapine	2A	HLA-B*35:01	Drug Hypersensitivity (rash)	Mixed population	Increased (reported to be depend on CD4 T-cells count)	N/A RNPGx reco: no indication in routine care
	2B	HLA-DRB1*01:01	Drug hypersensitivity (hepatitis)	Mixed population	Increased	
	3	HLA-B*35:01	Drug hypersensitivity (rash)	Asian (Thai)	Increased (reported to be depend on CD4 T-cells count)	
	3	HLA-DQB1*05:01	Drug hypersensitivity (various manifestations)	Black or African American	Decreased	

Table 1 (*Continued*)

Drug	Level of evidence [29]	Allele	Clinical manifestation	Population	Risk of ADR	Clinical implementation [29,32,33] French National Pharmacogenetics network (RNPGx) recommendations
Nonsteroidal anti-inflammatory drugs	3	HLA-DR11	Anaphylactoid reactions	Spain	Increased	N/A RNPGx reco: no indication in routine care
Oxcarbazepine	3	HLA-B*13:02	MEP	Asian (Chinese)	Increased	N/A
	3	HLA-B*15:02	MEP, SJS/TEN	Asian	Increased	RNPGx reco: no indication in
	3	HLA-B*15:19; HLA-B*15:27; HLA-B*27:09; HLA-B*38:02; HLA-B*48:04	MEP	Asian (Han Chinese)	Increased	routine care
	4	HLA-B*15:18:01/*40:01:01 genotype	SJS/TEN	Mixed population	Increased	N/A RNPGx reco: no indication in routine care
Pegylated interferon and ribavirin	3	HLA-B*38:01	Non-responder to therapy	Egyptian	N/A	DPWG: information about lower response in HLA-B*44 negative patients (no genotyping recommendations)
	3	HLA-B*44:02	Sustained response	Spain	N/A	RNPGx reco: no indication in routine care
Phenobarbital	3	HLA-B*51:01	SJS/TEN	Asian	Increased	N/A RNPGx reco: no indication in routine care
Phenytoin	1A	HLA-B*15:02	SJS/TEN	Asian	Increased	FDA: warning (no genotyping recommendations), CPIC: drug contraindicated for B*15:02 positive patients
	3	HLA-B*13:01	SJS/TEN	Asian	Increased (not increased in one study)	HLA-B*15:02 test: PPV = 33%, NPV = 100% RNPGx reco: HLA-B*15:02 advisable in Asian ancestry populations (Han Chinese and Taiwanese)
	3	HLA-B*56:02	DRESS	Indigenous Australian	Increased	
Sulfasalazine	3	HLA-B*39:01; HLA-B*13:01	DRESS	Asian	Increased	N/A RNPGx reco: no indication in routine care
	4	HLA-B*15:05	DRESS	Asian	Increased	

Table 1 (*Continued*)

Drug	Level of evidence [29]	Allele	Clinical manifestation	Population	Risk of ADR	Clinical implementation [29,32,33] French National Pharmacogenetics network (RNPGx) recommendations
Thioamides (carbimazole, methimazole, propylthiouracil)	2A	HLA-B*38:02:01	Agranulocytosis	Mixed population	Increased	N/A RNPGx reco: no indication in routine care
Ticlopidine	3	HLA-B*44:03	Hepatotoxicity and cholestatic hepatotoxicity	Asian	Increased	N/A RNPGx reco: no indication in routine care
Trichloroethylene	3	HLA-B*13:01	Hypersensitivity dermatitis	Asian (Chinese)	Increased	N/A RNPGx reco: no indication in routine care
Ustekinumab	3	HLA-C*06:02	Better response (psoriasis)	Caucasian	N/A	N/A RNPGx reco: no indication in routine care
Ximelagatran	N/A	DRB1*07:01, DQA1*02:01	Drug-induced liver injury	European	Increased	Withdrawn in 2006 following reports of hepatotoxicity
Zonisamide	3	HLA-A*02:07:01	SJS/TEN	Asian (Japanese)	Increased	N/A RNPGx reco: no indication in routine care

ACR: American College of Rheumatology; CPIC: Clinical Pharmacogenetics Implementation Consortium; CPNDS: Canadian Pharmacogenomics Network for Drug Safety; DPWG: Dutch Pharmacogenetics Working Group; DRESS: drug reaction with eosinophilia and systemic symptoms; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); HDRs: hypersensitivity drug reactions; MPE: maculopapular eruption; NPV: negative predictive value; OR: odds ratio; PMDA: Pharmaceuticals and Medical Devices Agency — Japan; PPV: positive predictive value; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis. RNPGx recommendations are categorized into 4 categories: essential, advisable, potentially usefull and no indication in routine care.

[a] See text for further details.

analyses that combined data obtain from different Asian population all found odds ratios of approximately 80 for carbamazepine-induced SJS/TEN in patients carrying the HLA-B*15:02 allele [54—56]. A 2011 large prospective study, intended to evaluate the value of HLA-B*15:02 genotyping before carbamazepine treatment, demonstrated that SJS/TEN did not develop in any of the treated patients if the subjects were HLA-B*1502-negative. Considered an expected incidence of 0.23% based on historical data, the genetic screening successfully prevented 10 cases of HDR [57]. These results paved the way for the implementation of HLA-B*15:02 screening before carbamazepine therapy in Asian patients. Nevertheless, HLA-B*15:02 has not been found to be a risk factor in Caucasian or Japanese populations, probably because of the very low prevalence of this allele in these ethnic group (1% or less). In European or Japanese recent data suggests that carbamazepine-related HDRs, including SJS/TEN, MPE, and DRESS, are associated with the presence of the HLA-A*31:01 allele [54,58—61]. Interestingly, in Han Chinese, HLA-A*31:01 allele has been associated with an increased risk of carbamazepine-induced MPE or DRESS, while HLA-B*15:02 is related only to SJS/TEN [27,46,54]. These observations suggest that genetic susceptibility to carbamazepine-related HDRs, at least in certain populations, seems to be phenotype-specific. Beyond HLA-B*15:02 and HLA-A*31:01, other HLA alleles have been associated to an increased risk of carbamazepine-related HDRs in various populations (Table 1), nevertheless these studies are limited and need further confirmation. At this time, FDA recommends HLA-B*15:02 genetic testing prior to a carbamazepine based treatment in individuals of Asian ethnicity [32,33]. A warning has been added to the prescribing information by FDA indicating that the risks and benefits of using carbamazepine should be weighed in HLA-A*31:01 allele carriers [33]. Different reports put HLA-B*15:02 in relation also with SJS/TEN induced by aromatic antiepileptic drugs, other than carbamazepine, such as phenytoin, oxcarbazepine and lamotrigine [7,46,54,62]. These findings suggest that HLA-B*15:02 positive patients may show cross-reactivity to structurally related anticonvulsants and consequently special attention should be given when considering antiepileptic treatment for HLA-B*1502 allele carriers [63]. Currently, FDA advise to avoid phenytoin as alternative for carbamazepine in HLA-B*1502 positive patients, although it does not make specific recommendations for other structurally-related anticonvulsant [33].

Allopurinol

Allopurinol is a xanthine oxidase inhibitor used to treat disorders associated with hyperuricemia, such as chronic gout and tumor lysis syndrome. The most serious ADRs associated to allopurinol are HDRs, which include DRESS and SJS/TEN and occur in approximately 0.1—0.4% of treated patients [64]. Allopurinol is the most frequent cause of SJS/TEN in Europe, exceeding carbamazepine and phenytoin, while in southeast Asia, is the second most common SJS/TEN-causative drug after carbamazepine [45,65].

In 2005, a case-controlled study reported that a specific HLA allele, HLA-B*58:01, was present in 100% of patients with allopurinol-induced HDRs compared to 15% of allopurinol-tolerant patients and 20% of healthy controls [66]. Similar results have been replicated in other ethnic groups: strong association was reported in Han Chinese, Thais, Japanese and Koreans while weaker association was described in Europeans [67—72]. This differences probably reflect the different prevalence of HLA-B*58:01 which is higher in Asian populations as compared to Europeans and/or additional contributing factors not yet elucidated. However, a recent meta-analysis found a strong and significant association the HLA-B*58:01 allele and allopurinol-induced SJS/TEN (OR 96.60 and OR 79.28 in studies with matched-control or population-control, respectively) in both Asian and non-Asian populations [73]. In the light of the strong association of HLA-B*58:01 with hypersensitivity reactions to allopurinol across different populations, a genetic screening of patients prior to initiating allopurinol will be most likely adopted in future. To date, FDA and EMA have not implemented allopurinol labeling information for HLA-B*58:01 testing. The Clinical Pharmacogenetics Implementation Consortium guidelines recommend that allopurinol should not be prescribed to patients who are positive for the HLA-B*5801 allele but underline that negative testing does not exclude the possibility of developing SCARs, especially in European populations [64]. The 2012 revised guidelines of the American College of Rheumatology also recommend HLA-B*58:01 screening prior to allopurinol prescription, especially in those populations with high frequencies of the allele, such as the Han Chinese or Thais [74].

Conclusion

Abacavir, carbamazepine, and allopurinol are key examples of pharmacogenetics implementation in routine medical practice (Table 2) [75], but many other HLA-related HDRs have been reported so far (Table 1). However, several considerations should be taken into account before such associations could be translated in cost-effective screening procedures, these factors have been recently reviewed by Phillips and Mallal [76]. Premises for a successful implementation of a given HLA pharmacogenetic testing into routine clinical care requires that: drug toxicity is severe and persistent, the NPV (and ideally also the PPV) of the test reach 100%, culprit HLA allele is prevalent inside the screened population, and the number of patients needed to test in order to prevent a case is low. In addition, responsible drug should have good efficacy, cost-effectiveness and, tolerability, in the absence of alternative drug(s) with similar positive characteristics. Flucloxacillin-related liver toxicity can be cited as a paradigmatic example, although strongly associated with HLA-B*57:01 allele (OR 80), almost 14,000 patients should be tested to prevent a single case of hepatotoxicity, making this screening neither cost-effective nor feasible [34,77]. In view of this, only few HLA-disease-drug associations reported to date will be reasonably translated into routine clinical practice.

Nevertheless, clinical value of pharmacogenetic markers is not only limited to predict susceptibility to HDR in pre-treatment setting but may also be exploited as tests of exclusion, as has been proposed for the re-introduction of lumiracoxib, or differential diagnosis tools, as has been suggested for flucloxacillin-induced hepatitis [78]. Due

Table 2 Main genetic variants discussed in this article.

Gene[a]	Name[a]	Polymorphism[a]	Reference rs	Common name of the allele	Frequency of HLA alleles across diverse populations [75]	In vitro function	In vivo function
Histocompatibility complex (Chromosome 6p21.3)	Major histocompatibility complex, class I, A	*57:01	N/A	HLA-B*57:01	West Europe: 5—10%, Mediterranean: 1—4%, UK: 5—10%, Middle East: 1—4%, US Caucasian: 5—10%, US Asia: 1—3%, US African-American: 2—3%, US Hispanic: 1—5%, South American Caucasian: 5—10%, Sub-Saharan Africa: < 1%, Australia: 5—10%, Thailand: 5—10%, China: < 1%, Japan: < 1%, India: 5—15%	N/A	N/A
		*58:01	N/A	HLA-B*58:01	West Europe: 1—4%, Mediterranean: 1—4%, UK: < 1%, Middle East: 5—10%, US Caucasian: 1—4%, US Asia: 5—10%, US African-American: 5—10%, US Hispanic: 1—4%, South American Caucasian: 1—4%, Sub-Saharan Africa: 5—15%, Australia: 1—4%, Thailand: 5—15%, China: 5—20%, Japan: < 1%, India: 5—15%	N/A	N/A
		*15:02	N/A	HLA-B*15:02	West Europe: < 1%, Mediterranean: < 1%, UK: < 1%, Middle East: < 1%, US Caucasian: < 1%, US Asia: 5—10%, US African-American: < 1%, US Hispanic: < 1%, South American Caucasian: < 1%, Sub-Saharan Africa: < 1%, Australia: < 1%, Thailand: 10—20%, China: 5—20%, Japan: < 1%, India: 5—15%	N/A	N/A

From a practical point of view, HLA genotyping test for drug hypersensitivity should be interpreted as follow. Since HLA expression is co-dominant, results are reported as either ''positive'' or ''negative'', with no intermediate phenotype. The absence of the tested alleles (reported as ''negative'' on a genotyping test) indicates that the patient has a very low risk of HDR. On the opposite, ''positive'' result (heterozygote and homozygous variants) means that the drug is contraindicated due to the increased risk of drug-induced hypersensitivity [39]. N/A: not applicable.

[a] HGNC-approved gene nomenclature (see http://www.genenames.org).

to their pharmacological unpredictability and very low incidence, HDRs are usually recognized in the post-marketing phase of the drug life cycle leading to product withdrawal after important investment has been made in research and development. A systematic DNA banking during drug development phase could allow, if a HDR occurs, to retrospectively research a susceptibility genomic biomarker. In this context, successful identification of a predictive marker could avert withdrawal of the drug from the market by limiting the use of the drug to genetically tolerant subjects [79]. Last but not least, progresses in basic research on immunological mechanisms involved in HDRs could improve drug design, and lay the groundwork for the development of in vitro tests capable to identify harmful compounds in preclinical phases of drug development. These implementations would increase drug safety by predicting HDRs before their use in man, and, at the same time, would greatly reduce the cost of drug development [80].

Disclosure of interest

The authors declare that they have no competing interest.

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