Review

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An update on *HLA* alleles associated with adverse drug reactions

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Abstract: Adverse drug reactions (ADRs) are considered as an important cause of morbidity and mortality. The hypersensitivity reactions are immune-mediated ADRs, which are dose-independent, unpredictable and have been associated with several *HLA* alleles. The present review aimed to describe *HLA* alleles that have been associated with different ADRs in populations worldwide, the recommendations of regulatory agencies and pharmacoeconomic information and databases for the study of *HLA* alleles in pharmacogenetics. A systematic search was performed in June 2016 of articles relevant to this issue in indexed journals and in scientific databases (PubMed and PharmGKB). The information of 95 association studies found was summarized. Several *HLA* alleles and haplotypes have been associated with ADRs induced mainly by carbamazepine, allopurinol, abacavir and nevirapine, among other drugs. Years with the highest numbers of publications were 2013 and 2014. The majority of the reports have been performed on Asians and Caucasians, and carbamazepine was the most studied ADR drug inducer. Two *HLA* alleles' databases are described, as well as the recommendations of the U.S. Food and Drug Administration, the European Medicine Agency and the Clinical Pharmacogenetics Implementation Consortium. Pharmacoeconomic studies on this issue are also mentioned. The strongest associations remain for *HLA-B*58:01*, *HLA-B*57:01*, *HLA-B*15:02* and *HLA-A*31:01* but only in certain populations; therefore, studies on different ethnic groups would be useful. Due to the improvement of drug therapy and the economic benefit that *HLA* screening represents, investigations on *HLA* alleles associated with ADR should continue.

Keywords: abacavir; allopurinol; adverse drug reactions; carbamazepine; human leukocyte antigen (HLA); hypersensitivity syndrome; pharmacogenetics; Stevens-Johnson syndrome.

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Introduction

Immunologic-mediated adverse drug reactions (ADRs) are included in type B ADRs which are not related to the dose and that are uncommon and unpredictable in that they are not related with the pharmacodynamics of the drug and present high mortality [1]. There is evidence that susceptibility to at least some Type B ADR is found under strong genetic influence [2], and identifying genetic risk factors for this type of ADRs could significantly decrease healthcare costs and improve the process of drug development [3].

The drug-activated immune response is known to be mediated by T cells when the drug molecule binds to T-cell receptors (TCR). The majority of existing drug molecules have a comparable size of one to three amino acids, which is much smaller than the peptide ligands of human leukocyte antigen (HLA) class I (8–12 mers) and class II (9–25 mers) molecules [4]. Accordingly, the following five hypotheses have been proposed in order to explain T-cell recognition of a drug antigen presented by a HLA molecule: (i) the hapten/pro-hapten theory, (ii) the p.i. concept, (iii) the "altered repertoire" model, (iv) the "altered T-cell receptor repertoire" model and (v) the danger hypothesis [4–6] (Figure 1).

Briefly, the first hypothesis postulates that the drug or its immunogenic metabolite binds by covalent bonds to an endogenous peptide and to the HLA molecule, which particularly explains the hypersensitivity to beta-lactam antibiotics. The p.i. ("pharmacological interaction with the immune receptor") concept considers a non-covalent and reversible binding of the molecule directly to the HLA

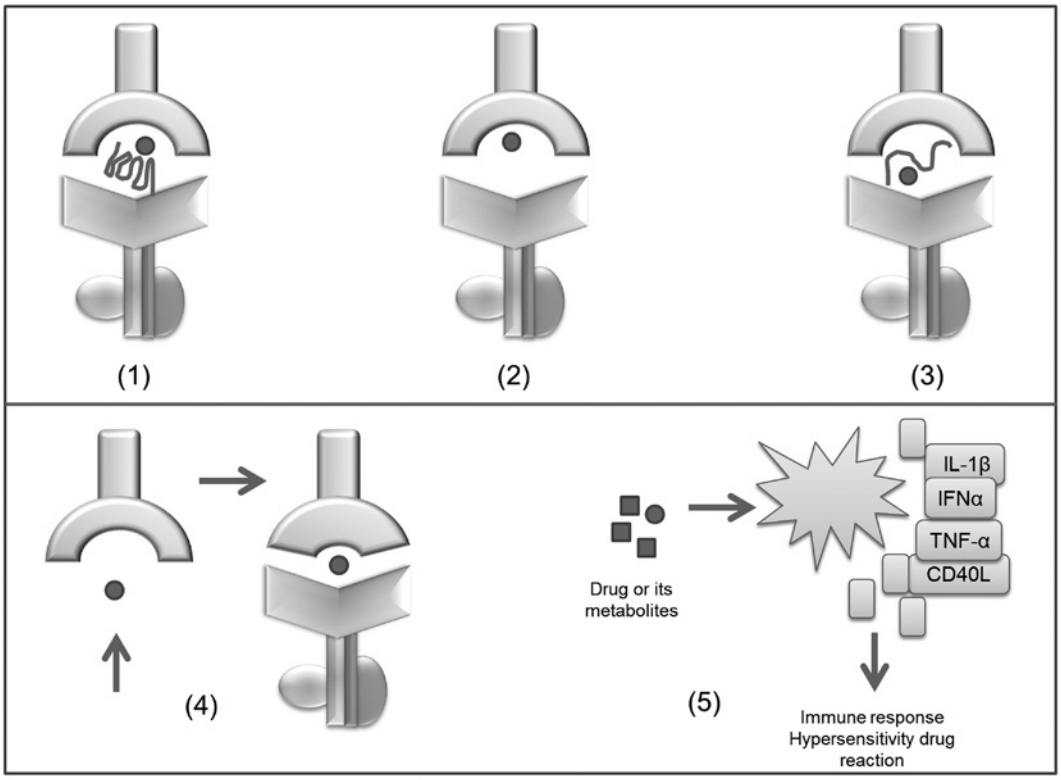

Figure 1: Models of drug interactions with immunology molecules.
(1) Hapten/pro-hapten theory, (2) p.i. concept, (3) "altered repertoire" model, (4) "altered T-cell receptor repertoire" model and (5) danger hypothesis.

molecule and/or the TCR, which could be the case for carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and the *HLA-B*15:02* allele. The "altered repertoire" model proposes that a drug can non-covalently bind to the self-peptide repertoire and alter the conformation of this peptide repertoire presented to HLA and TCR protein, inducing cutaneous adverse drug reactions (cADRs); in this case, the drug may not directly bind to HLA, and this hypothesis elucidates in part the association of *HLA-B*57:01* and abacavir-induced cADRs. The "altered TCR repertoire" model suggests that the drug interacts first with the TCR, which undergoes a conformational change that, in turn, allows binding with an HLA molecule to induce the immune response. Finally, the danger hypothesis explains that immune responses are caused by endogenous cellular alarm signals (i.e. CD40L, TNF-α, IL-1β and IFN-α) from distressed or injured cells, which could occur after the processing of the drug as antigen [4–6].

As mentioned previously, several *HLA* alleles have been associated with different induced ADRs. The majority of these are related with cADRs, which comprise mild ailments such as maculopapular exanthema (MPE) and severe syndromes such as the SJS, toxic epidermal necrolysis (TEN) and the drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) [6, 7]. Furthermore, there are reports that also support the implication of variations in immune genes with drug-induced liver injury (DILI) [8–12], drug-induced proteinuria [13] and agranulocytosis [14].

The most common descriptions of associations of *HLA* alleles with ADRs were reported for *HLA-B*15:02* and CBZ-induced SJS [15], *HLA-B*58:01* and allopurinol-induced SJS or DIHS [16] and *HLA-B*57:01* with a hypersensitivity reaction to abacavir [17]. Over time, several association studies have been performed in different populations, and some of these have described that the associated *HLA* allele is drug-specific and that ethnicity matters [18]. Moreover, guideline recommendations by regulatory agencies have been published in order to prevent different cADRs by means of *HLA* genotyping prior to drug prescription, and databases are now available to supply information on *HLA* alleles associated with ADR throughout the world. Therefore, in the light of these advances in *HLA* alleles in ADRs the present review

aimed to describe *HLA* alleles that have been associated with several ADRs in worldwide populations, the recommendations of regulatory agencies, pharmacoeconomic information and databases for the study on *HLA* alleles in pharmacogenetics.

Methods

We performed a systematic search in June 2016 of relevant articles for this issue in indexed journals and scientific databases (PubMed and PharmGKB). Search words included "HLA and adverse drug reactions". Association studies in which at least one *HLA* allele was related with the risk of ADR occurrences were included in the corresponding section. Articles were selected according to their relevance on the subject. The whole body of information was analyzed and summarized.

HLA alleles associated with adverse drug reactions

Ninety-five articles reporting that *HLA* alleles have been associated with ADRs were selected, and the main information of the association study was summarized in Table 1 for CBZ-induced cADRs, Table 2 for *HLA* alleles related to other antiepileptic drugs-induced cADRs, Table 3 for allopurinol, abacavir and nevirapine studies with *HLA* and ADRs and Table 4 for reports of *HLA* alleles in ADRs produced by different drugs.

The association of *HLA* alleles with CBZ-induced cADRs has been widely reported for several populations, including Asians (Han Chinese, Japanese, Korean, Thai, Malaysian, Indian, Vietnamese and Singaporean), European, North American and Mexican mestizos. The most significant associations have been described for *HLA-B*15:02* allele in Asian populations; however, important associations have been found for the *HLA-A*31:01* allele in European, North American, Mexican mestizos and Japanese populations. Other alleles associated with CBZ-induced cADRs are *HLA-A*01:01:01*, *-A*02:01*, *-DRB1*14:05*, *-B*51:01*, *-B*15:11*, *-A*02:06*, *-A*24:02*, *-C*08:01* and *-DRB1*12:02* (Table 1). The *HLA-B*15:02* allele also has been associated with other antiepileptic drugs-induced cADRs, such as phenytoin and oxcarbazepine. In addition, other *HLA* alleles have exhibited an association with lamotrigine-, phenobarbital-, phenytoin- and zonisamide-induced cADRs (Table 2).

Several investigations have found a strong association of *HLA-B*58:01* with cADRs induced by allopurinol, mainly in patients with Asian ancestry; however, there are also reports that include European and Portuguese populations in whom this allele has also been associated. Other alleles that have been related with allopurinol-induced cADRs include *HLA-C*03:02* and *-A*33:03* in Koreans and *HLA-DRB1*15:02* and *-DRB1*13:02* in Caucasians. Studies of abacavir hypersensitivity have been mostly performed in Caucasians from the U.S. and Australia. The main associated *HLA* allele is *HLA-B*57:01*, and only one study (to our knowledge) has reported the association of two different alleles from *HLA* class II (*HLA-DR7* and *-DQ3*) with abacavir-induced hypersensitivity. For nevirapine, four different *HLA* alleles in four studies have been found associated with ADRs induced by this drug; two of these reports identified an association between the *HLA-C*04* allele and hypersensitivity in Han Chinese and SJS/NET in Malawian patients. There are also reports that have investigated the relation of *HLA* alleles with hepatotoxicity induced by this drug (Table 3).

There are several reports of other *HLA* alleles associated with other different drugs-induced ADRs, for instance, amoxicillin-clavulanate, antituberculosis drugs, asparaginase, aspirin, clozapine, cold medications, co-trimaxole, dapsone and penicillins, among others. The type of ADRs included in these studies comprises hypersensitivity, cADR, drug-induced liver injury, proteinuria, agranulocytosis and other specific reactions, such as aspirin-exacerbated respiratory disease and cold medicine-related SJS/TEN with severe ocular-surface complications. In some cases, the studies have only been performed in one population, and the information remains not sufficiently strong to be considered in clinical recommendations (Table 4).

The studies included comprise years of publication from 1993 to 2016 with at least one study reporting an association between *HLA* alleles and ADRs published per year. The highest number of reports was published in 2013 and 2014 (13 per year), which is 6 years after the U.S. Food and Drug Administration (FDA) recommendation on genetic screening for patients of Asian ancestry prior to the initiation of CBZ therapy [112] and when the number of studies in this subject increased. The majority of the investigations have studied CBZ-induced cADRs (29%), followed by allopurinol- and lamotrigine-induced cADRs (13% and 7%, respectively). Few studies have been performed for abacavir- and phenytoin-induced hypersensitivity (6% for each) and for ADRs induced by amoxicillin-clavulanate, nevirapine and oxcarbazepine (4% for each). Fifty-five percent of the studies have included

Table 1: *HLA* alleles associated with carbamazepine-induced cutaneous adverse drug reactions.

ADR type	Population	*HLA* allele	n +/tot	OR	95% CI	p-Value	References
cADR	Japanese	*-A*31*	10/15	11.20	2.668–47.105	0.001	[19]
cADR	Japanese	*-A*31:01*	37/61	10.80	5.9–19.6	3.64×10^{-15}	[20]
DRESS	European	*-A*31:01*	7/10	57.60	11.0–341.0	<0.001	[21]
DRESS	Chinese	*-A*31:01*	5/10	23.00	4.2–125	<0.001	[21]
HSS	North American	*-A*31:01*	3/6	26.36	2.53–307.89	0.002	[22]
HSS	European	*-A*31:01*	10/27	12.41	1.27–121.03	3.5×10^{-8}	[23]
MPE	Mexican mestizo	*-A*01:01:01*	3/5	7.29	1.02–52.01	0.028	[24]
MPE	Mexican mestizo	*-A*31:01:02*	2/5	ND	ND	0.006	[24]
MPE	Han Chinese	*-A*02:01*	11/80 (2n)	ND	ND	0.033	[25]
MPE	Han Chinese	*-DRB1*14:05*	7/80 (2n)	ND	ND	0.003	[25]
MPE	North America	*-A*31:01*	6/26	8.57	1.67–57.50	0.004	[22]
MPE	European	*-A*31:01*	23/106	8.33	3.59–19.36	8.0×10^{-7}	[23]
MPE/DRESS	Han Chinese	*-A*31:01*	14/74	6.86	2.4–19.9	2.7×10^{-3}	[26]
MPE/DRESS	Han Chinese	*-B*51:01*	18/74	4.56	2.0–10.5	0.01	[26]
MPE/HSS	Chinese	*-A*31:01*	8/31	12.17	3.6–41.2	0.0021	[27]
SCAR	Japanese	*-A*31:01*	11/44 (2n)	4.33	2.07–9.06	0.0004	[28]
SJS	Han Chinese	*-B*15:02*	44/44	2504	126–49,522	3.1×10^{-27}	[15]
SJS	North American	*-B*15:02*	3/9	38.65	2.68–2239.5	0.002	[22]
SJS	Chinese and Malaysian	*-B*15:02*	6/6	ND	ND	0.0345	[29]
SJS	Korean	*-B*15:11*	3/7	18.00	2.3–141.2	0.011	[30]
SJS	Indian	*-B*15:02*	6/8	71.40	3.0–1698	0.0014	[31]
SJS	Thai	*-B*15:02*	6/6	25.50	2.68–242.61	0.0005	[32]
SJS/TEN	Vietnamese	*-B*15:02*	32/38	33.78	7.55–151.03	<0.001	[33]
SJS/TEN	Han Chinese	*-B*15:02*	24/26	89.25	19.25–413.83	3.51×10^{-18}	[34]
SJS/TEN	North Indian	*-B*15:02*	2/9	ND	ND	0.035	[35]
SJS/TEN	Han Chinese	*-B*15:02*	8/35	18.22	3.66–90.66	0.000	[36]
SJS/TEN	Singaporean	*-B*15:02*	13/13	181.00	8.7–3785	6.9×10^{-8}	[37]
SJS/TEN	Chinese	*-B*15:02*	41/53	58.10	17.6–192	<0.001	[21]
SJS/TEN	Singaporean	*-B*15:02*	5/5	27.20	2.67 to ∞	<0.05	[38]
SJS/TEN	Han Chinese	*-B*15:02*	24/26	89.25	19.25–413.83	3.51×10^{-18}	[39]
SJS/TEN	Japanese	*-A*02:06*	51/110	5.07	ND	6.9×10^{-10}	[40]
SJS/TEN	Han Chinese	*-A*24:02*	9/16	3.18	1.11–9.11	0.03	[41]
SJS/TEN	Han Chinese	*-B*15:02*	13/18	17.55	5.31–58.06	<0.001	[41]
SJS/TEN	Thai	*-B*15:02*	32/34	75.40	13.0–718.9	<0.001	[42]
SJS/TEN	European	*-A*31:01*	5/12	25.93	4.93–116.18	8.0×10^{-5}	[23]
SJS/TEN	Han Chinese	*-B*15:02*	16/17	152.00	12–1835	<0.0001	[43]
SJS/TEN	Han Chinese	*-B*15:02*	9/9	114.83	6.25–2111.03	<0.001	[44]
SJS/TEN	Malaysian	*-B*15:02*	12/17	16.15	4.57–62.4	7.87×10^{-6}	[45]
SJS/TEN	Japanese	*-B*15:11*	4/28	16.30	4.76–55.6	0.0004	[46]
SJS/TEN	Chinese	*-B*15:02*	8/8	184.00	33.2–1021.0	<0.05	[47]
SJS/TEN	Thai	*-B*15:02*	37/42	54.76	14.62–205.13	2.89×10^{-12}	[48]
SJS/TEN	Chinese	*-B*15:02*	59/60	1357.00	193.4–8838.3	1.6×10^{-41}	[27]
SJS/TEN	Chinese	*-C*08:01*	56/60	86.80	29.3–254.6	7.8×10^{-27}	[27]
SJS/TEN	Chinese	*-DRB1*12:02*	41/60	11.40	5.6–22.9	2.3×10^{-11}	[27]
SJS/TEN >5% skin detachment	Han Chinese	*-B*15:02*	25/25	97.60	42.0–226.8	5.8×10^{-43}	[26]

ADR, adverse drug reaction; cADR, cutaneous adverse drug reaction; CI, confidence interval; DRESS, drug reactions with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; ND, not determined; n +/tot, number of subjects positive for the *HLA* allele associated/total of subjects included in the association study; OR, odds ratio; SCAR, severe cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Asian patients in whom there is a notably higher incidence of cADRs than in Caucasians [113]; however, an important percentage of these reports was also performed in individuals of Caucasian ancestry (42%); Africans have only been included in one study and individuals from America in three.

Table 2: *HLA* alleles associated with antiepileptic drugs-induced cutaneous adverse drug reactions.

Drug	ADR	Population	*HLA* allele	n +/tot	OR	95% CI	p-Value	References
Antiepileptic drugs	SJS/TEN	Han Chinese	*-B*15:02*	6/6	71.9	3.7–1,415.8	1.48×10^{-4}	[49]
	SJS/TEN	Han Chinese	*-B*15:02*	15/27	18.75	5.29–66.44	0.000	[50]
Lamotrigine	cADR	Norwegian	*-A*24:02*	10/28	ND	ND	0.027	[51]
	cADR	Japanese	*-DRB1*04:05*	6/16	ND	ND	0.01	[52]
	cADR	Japanese	*-DQB1*04:01*	6/16	ND	ND	0.01	[52]
	MPE	Korean	*-A*24:02*	15/21	4.09	1.22–13.69	0.025	[53]
	MPE	Korean	*-A*24:02/ -C*01:02*	10/21	7.88	1.81–34.28	0.007	[53]
	MPE	Mexican mestizo	*-A*02:01:01/ -B*35:01:01/ -C*04:01:01*	4/10	18.33	1.99–169.08	0.0048	[24]
	MPE	Han Chinese	*-A*30:01*	6/86 (2n)	ND	ND	0.013	[25]
	MPE	Han Chinese	*-B*13:02*	6/86 (2n)	ND	ND	0.013	[25]
	SCAR	European	*-A*68:01*	4/44 (2n)	19.22	1.01–365	0.012	[54]
	SJS/TEN	Korean	*-B*44:03*	3/5	ND	ND	0.099	[55]
Oxcarbazepine	MPE	Han Chinese	*-B*38:02*	3/28 (2n)	3.33	1.78–22.46	0.018	[56]
	MPE	Han Chinese	*-B*13:02*	4/28 (2n)	7.83	2.32–26.41	0.001	[57]
	MPE	Han Chinese	*-B*15:02*	4/9	8.8	1.85–41.79	0.011	[58]
	SJS	Han Chinese	*-B*15:02*	3/3	80.7	3.8–1714.4	8.4×10^{-4}	[59]
Phenobarbital	SJS/TEN	Japanese	*-B*51:01*	6/8	16.71	3.66–83.06	0.004	[60]
Phenytoin	DRESS	Malay	*-B*15:13*	3/3	59	2.49–1395.74	0.003	[61]
	MPE	Mexican mestizos	*-C*08:01*	2/2	ND	ND	0.002	[24]
	SJS	Thai	*-B*15:02*	4/4	18.5	1.82–188.40	0.005	[32]
	SJS/TEN	Malay	*-B*15:13*	7/13	11.28	2.25–59.60	0.003	[61]
	SJS/TEN	Malay	*-B*15:02*	8/13	5.71	1.41–23.10	0.016	[61]
	SJS/TEN	Han Chinese	*-B*15:02*	7/15	3.44	1.08–11.00	0.047	[34]
	SJS/TEN	Han Chinese	*-B*15:02*	7/15	3.5	1.10–11.18	0.045	[39]
	SJS/TEN	Han Chinese	*-B*15:02*	8/26	5.1	1.8–15.1	0.0041	[59]
	SJS/TEN	Han Chinese	*-B*13:01*	9/26	3.7	1.4–10.0	0.0154	[59]
	SJS/TEN	Han Chinese	*-C*08:01*	9/26	3	1.1–7.8	0.0281	[59]
	SJS/TEN	Han Chinese	*-DRB1*16:02*	7/26	4.3	1.4–12.8	0.0128	[59]
Zonisamide	SJS/TEN	Japanese	*-A*02:07*	5/12	9.77	3.07–31.1	0.018	[60]

ADR, adverse drug reaction; cADR, cutaneous adverse drug reaction; CI, confidence interval; DRESS, drug reactions with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; MPE, maculopapular exanthema; ND, not determined; n +/tot, number of subjects positive for the *HLA* allele associated/total of subjects included in the association study; OR, odds ratio; SCAR, severe cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Databases with *HLA* alleles and adverse drug reactions

As can be observed in Tables 1–4, several class I and II *HLA* alleles have been associated with ADRs in different populations. The *HLA* allele associated in a certain ethnic group is largely influenced by the frequency of the specific allele among the studied population [18, 114]. In order to facilitate the investigation and associations of *HLA* alleles and ADRs, two databases have been designed [115, 116]. Both of these permit easy and rapid access to relevant information about a specific drug, ADR or *HLA* allele related with ADR pharmacogenomics.

One of these belongs to the Allele Frequency Net Database (http://www.allelefrequencies.net), a free, centralized resource that contains information on the allele, the haplotype and the genotype frequencies of several immune genes, including *HLA* alleles, in different populations [117]. This website was released in 2003 [118], and since then, the database has grown significantly in terms of the number of populations covered and the number of users and citations [115]. Therefore, to assist HLA and pharmacogenetic studies, this database contains collated data sets from the literature, with information that not only facilitates meta-analyses but that also enables users to examine the quality of published studies by comparing the frequencies of *HLA* alleles reported in healthy volunteers' cohorts with those

Table 3: *HLA* alleles associated with adverse reactions induced by allopurinol, abacavir and nevirapine.

Drug	ADR	Population	*HLA* allele	n +/tot	OR	95% CI	p-Value	References
Allopurinol	cADR	Japanese	*-B*58:01*	4/7	65.6	2.9–1497.0	9.73×10^{-4}	[62]
	cADR	Han Chinese	*-B*58:01*	38/38	580.07	32.18–10456.80	7.01×10^{-18}	[63]
	MPE	Han Chinese	*-B*58:01*	26/40	8.5	4.2–17.5	2.3×10^{-9}	[64]
	SCAR	Han Chinese	*-B*58:01*	96/106	44	21.5–90.3	2.6×10^{-41}	[64]
	SCAR	Han Chinese	*-B*58:01*	87/92	127.6	40.8–398.6	<0.001	[65]
	SCAR	Han Chinese	*-B*58:01*	45/48	108.5	33.7–346.3	<0.0001	[66]
	SCAR	Portuguese	*-B*58:01*	16/25	39.11	4.49–340.51	5.9×10^{-4}	[67]
	SCAR	Han Chinese	*-B*58:01*	19/19	229.7	11.7–4520.4	<0.0001	[68]
	SCAR	Korean	*-B*58:01*	23/25	97.8	18.3–521.5	2.45×10^{-11}	[69]
	SCAR	Korean	*-C*03:02*	23/25	82.1	15.8–426.5	9.39×10^{-11}	[69]
	SCAR	Korean	*-A*33:03*	22/25	20.5	5.4–78.6	3.31×10^{-6}	[69]
	SCAR	Han Chinese	*-B*58:01*	51/51	580.3	34.4–9780.9	4.7×10^{-24}	[16]
	SCAR	Caucasian	*-B*58:01*	3/7	13.6	2.77–69.45	0.003	[70]
	SCAR	Caucasian	*-DRB1*15:02*	2/7	22.6	3.28–160.72	0.005	[70]
	SCAR	Caucasian	*-DRB1*13:02*	2/7	11.1	1.94–7.64	0.037	[70]
	SJS/TEN	Korean	*-B*58:01*	5/7	ND	ND	0.013	[71]
	SJS/TEN	Thai	*-B*58:01*	27/27	348.3	19.2–6336.9	<0.001	[72]
	SJS/TEN	Japanese	*-B*58:01*	4/20 (2n)	40.83	10.5–158.9	<0.0001	[73]
	SJS/TEN	European	*-B*58:01*	15/27	80	34–187	$<10^{-6}$	[74]
Abacavir	AHS	Caucasian	*-B*57:01*	18/20	6934	321–149,035	<0.0001	[75]
	AHS	White from U.S.	*-B*57:01*	42/42	1945	110–34,352	<0.0001	[17]
	AHS	Black from U.S.	*-B*57:01*	5/5	900	38–21,045	<0.0001	[17]
	AHS	Caucasian	*-B*57:01*	7/7	ND	ND	<0.001	[76]
	AHS	Western Australian	*-B*57:01*	17/18	960	NS	<0.00001	[77]
	AHS	North American	*-B*57*	39/84	23.6	8.0–70.0	<0.01	[78]
	AHS	Western Australian	*-B*57:01*	14/18	117	29–481	<0.0001	[79]
	AHS	Western Australian	*-B*5701*, *-DR7*, *-DQ3*	13/18	822	43–15,675	<0.0001	[79]
Nevirapine	cADR	Thai	*-B*35:05*	25/243	18.96	4.87–73.44	4.6×10^{-6}	[80]
	Hepatotoxicity	South African	*-B*58:01*	12/51	ND	ND	0.033	[81]
	Hepatotoxicity	South African	*-DRB1*01:02*	8/51	ND	ND	0.044	[81]
	Hypersensitivity	Han Chinese	*-C*04*	8/64	3.61	1.13–11.49	0.03	[82]
	SJS/TEN	Malawian	*-C*04:01*	23/36	17.52	3.31–92.8	NS	[83]
Nevirapine and Efavirenz	Hypersensitivity	French	*-DRB1*01*	5/6	ND	ND	0.04	[84]

ADR, adverse drug reaction; AHS, abacavir hypersensitivity; cADR, cutaneous adverse drug reaction; CI, confidence interval; HLA, human leukocyte antigen; MPE, maculopapular exanthema; ND, not determined; NS, not specified; n +/tot, number of subjects positive for the *HLA* allele associated/total of subjects included in the association study; OR, odds ratio; SCAR, severe cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

of worldwide populations. This resource only includes case-control studies with statistical evidence provided for the association and in which high-resolution *HLA* genotyping was performed. From each report, information about ethnicity, the drug of interest and the proportion of cases and controls carrying the *HLA* allele implicated in ADRs is extracted and summarized in the database [115].

The second of these is denominated the HLADR database (http://pgx.fudan.edu.cn/hladr/). This is an in-house database that manually collected the information of 1786 records after an extensive search and review of the literature and curation of reports of *HLA* alleles associated with ADRs. The information compiled from each report contains the following: drugs, ADRs, *HLA* alleles, the ethnic and geographic origins of the study subjects, a 2×2 contingency table reflecting the association strengths (p-value, odds ratio [OR], sensitivity, specificity, positive-predictive values and negative-predictive values) and FDA drug-labeling changes resulting from the drug-HLA associations. The association strengths across different studies were incomparable because different statistical methods were applied in the original reports; consequently, the designers of this database performed the Fisher's exact test and the Haldane's modification to recalculate the p-value and the OR for each association study, respectively. In addition, this resource standardized the names of ADRs and *HLA* alleles based on reference databases such as PharmGKB and international ImMunoGeneTics (IMGT) project/HLA [116].

Table 4: *HLA* alleles associated with different adverse reactions induced by several drugs.

Drug	ADR	Population	*HLA* allele	n +/tot	OR	95% CI	p-Value	References
Amoxicillin-clavulanate	DILI	Spaniard	*-A*30:02*	11/75	6.7	2.8–15.9	5×10^{-5}	[85]
	DILI	European	*-DQB1*06:02*	NS	4.2	2.7–6.6	4.6×10^{-10}	[10]
	DILI	European	*-DRB1*15*	32/61	2.59	1.44–4.68	0.002	[86]
	DILI	Belgian	*-DRB1*15:01/ -DRB5*01:01/-DQB1*06:02*	20/35	ND	ND	<0.0002	[87]
Antituberculosis treatment	ATLI	Chinese	*-DQB1*05/*05*	10/88	4.56	0.98–21.22	0.053	[88]
	DIH	Indian	*-DQB1*02:01*	25/47	2.2	1.19–4.15	<0.01	[89]
	HSS	Korean	*-C*04:01*	7/60	6.9	2.20–21.66	0.0204	[90]
Asparaginase	Allergy	European descent	*-DRB1*07:01*	66/143	1.92	5 1.29–2.87	0.023	[91]
Aspirin	Aspirin desensitization related to AERD	Iranian	*-DQB1*03:02*	7/14	0.12	0.02–0.76	0.022	[92]
	AERD	Iranian	*-DQB1*03:02*	16/66 (2n)	5.49	2.40–12.59	<0.01	[93]
	AERD	Iranian	*-DQA1*03:01*	20/66 (2n)	2.9	1.49–5.67	<0.01	[93]
	AERD	Iranian	*-DRB4*	28/66 (2n)	2.94	1.61–5.36	<0.01	[93]
Benznidazole	Moderate and severe cADRs	Spaniard	*-B*3505*	5/11	NS	NS	0.033	[94]
Bucillamine	Proteinuria	Japanese	*-DRB1*08:02*	7/25	25.17	7.98–79.38	1.96×10^{-5}	[95]
	Proteinuria	Japanese	*-DQB1*04:02*	8/25	10.35	3.99–26.83	2.69×10^{-4}	[95]
Clozapine	Agranulocytosis	Non-Jewish Caucasian	*-DRB5*0201*	5/84 (2n)	22.15	1.74–∞	0.005	[96]
	Agranulocytosis	Jewish Caucasian	*-DRB1*04:02*, *-DRB4*01:01*, *DQB1*03:02*, *DQA1*03:01*, *DPB1*04:01*	11/24 (2n)	6.8	ND	0.02	[97]
Cold medications	CM-SJS/TEN with SOC	Indian	*-B*44:03*	12/20	12.25	3.57–42.01	2.14.E – 05	[98]
	CM-SJS/TEN with SOC	Brazilian	*-B*44:03*	10/39	2.74	1.12–6.71	0.0478	[98]
	CM-SJS/TEN with SOC	Korean	*-A*02:06*	11/31	3	1.18–7.57	0.0362	[98]
Co-trimaxole	SJS/TEN	Thai	*-B*15:02*	14/43	3.91	1.42–10.92	0.02	[99]
	SJS/TEN	Thai	*-C*06:02*	5/43	11.84	1.24–566.04	0.013	[99]
	SJS/TEN	Thai	*-C*08:01*	12/43	3.53	1.21–10.40	0.011	[99]
	SJS/TEN	Thai	*-B*15:02/-C*08:01*	11/43	4.87	1.48–17.22	0.004	[99]
Dapsone	HSS	Chinese descent	*-B*13:01*	65/76	20.53	11.55–36.48	6.84×10^{-25}	[100]
	DIHR	Southern Chinese	*-B*13:01*	18/20	122.1	23.5–636.2	6.038×10^{-12}	[101]
Flucloxacillin	DILI	European	*-B*57:01*	43/51	80.6	22.8–284.9	8.97×10^{-19}	[8]
Lapatinib	Liver injury	Majority White, not Hispanic/Latino	*-DRB1*07:01*	29/37	14.12	6.36–31.32	2.4×10^{-13}	[102]
Methazolamide	SJS/TEN	Han Chinese	*-B*59:01*	7/8	305	11.3–8259.9	6.3×10^{-7}	[103]
	SJS/TEN	Korean	*-B*59:01*	5/5	249.8	13.4–4813.5	<0.001	[104]
Multiple drugs	SJS/TEN with ocular complications	Japanese	*-A*02:06*	19/40	5.1	NS	<0.0005	[105]
NSAIDs	Anaphylactoid reaction	Spaniard	*-DR11*	25/42 (2n)	7.3	2.8–19.0	0.02	[106]

Table 4 (continued)

Drug	ADR	Population	*HLA* allele	n +/tot	OR	95% CI	p-Value	References
Penicillins	Immediate hypersensitive reaction	Han Chinese	*-DRB9*	9/37	ND	ND	0.019	[107]
	Urticaria		*-DRB9*	10/37	ND	ND	0.005	[107]
Salazosulfapyridine	DRESS	Han Chinese	*-B*13:01*	4/6	13	ND	0.004	[108]
Sodium aurothiomalate	Mucocutaneous side effects	NS	*-DR1*	11/16	ND	ND	0.004	[109]
Sulphasalazine	SLE-like symptoms	Caucasian	*-DRB1*03:01*	3/4	ND	ND	0.012	[110]
Ticlopidine	Hepatotoxicity	Japanese	*-A*33:03*	15/22	13.04	4.40–38.59	1.24×10^{-5}	[111]
	Cholestatic hepatotoxicity	Japanese	*-A*33:03*	12/14	36.5	7.25–183.82	7.32×10^{-7}	[111]

ADR, adverse drug reaction; AERD, aspirin-exacerbated respiratory disease; ATLI, antituberculer drug-induced liver injuries; cADR, cutaneous adverse drug reaction; CI, confidence interval; CM-SJS/TEN with SOC, cold medicine-related SJS/TEN with severe ocular-surface complications; DIH, drug-induced hepatotoxicity; DIHR, dapsone-induced hypersensitivity reactions; HLA, human leukocyte antigen; DILI, drug-induced liver injury; DRESS, drug reactions with eosinophilia and systemic symptoms; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; ND, not determined; NS, not specified; n +/tot, number of subjects positive for the *HLA* allele associated/total of subjects included in the association study; OR, odds ratio; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; TEN, toxic epidermal necrolysis.

International medicine agencies recommendations on *HLA* alleles and drug prescriptions

International medicine agencies as the FDA in the U.S. and the European medicine agency (EMA) have made recommendations based on evidence published about *HLA* alleles associated with ADRs in drugs such as CBZ, allopurinol, abacavir and phenytoin, among others. These data have been added to the specific drug-label information in order to improve the safety of the drug and to inform physicians about the usefulness of performing *HLA* genotyping prior to prescribing the drug [112, 119]. In addition, the clinical pharmacogenetics implementation consortium (CPIC) has published guidelines for the dosing of abacavir, allopurinol, CBZ and phenytoin considering the patient's *HLA* genotype [120–127]. Recommendations from the three previously mentioned international medicine agencies are summarized in Table 5. For abacavir, the international medicine agencies and the CPIC highly recommend *HLA* genotyping in all patients with HIV of any ethnicity prior the prescription of this drug and avoiding the administration of abacavir in patients who are carriers of the *HLA-B*57:01* allele. In contrast, for allopurinol there is no well-established recommendation for routine *HLA* testing, although EMA and CPIC consider that the prescription of allopurinol should be evaluated carefully if it is known that the patient is an *HLA-B*58:01* carrier. In the case of CBZ, genetic testing for *HLA* is recommended in patients with Asian ancestry or, specifically, for Han Chinese and Thai population, but the use of this antiepileptic is contraindicated in any patient positive for the *HLA-B*15:02* allele regardless of the patient's ancestry. In addition, the agencies recommend that the use of CBZ in patients carrying *HLA-A*31:01*, especially of Caucasian or Japanese origin, should be considered if the benefits are thought to exceed the risks. Additionally, the recommendation for antiepileptic drug prescription is to avoid phenytoin and, in some cases, oxcarbazepine, eslicarbazepine acetate and lamotrigine in patients positive for *HLA-B*15:02*.

Pharmacoeconomic perspective of *HLA* genotyping prior to drug prescription

Among the benefits of the use of pharmacogenomics in clinical practice are those of guiding the initial drug

Table 5: International medicine agencies' recommendations on *HLA* genotyping and drug hypersensitivity.

Drug	*HLA* allele	Publisher	Recommendation[a]	References
Abacavir	*-B*57:01*	FDA	All patients should be screened for the *HLA-B*57:01* allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented *HLA-B*57:01* allele assessment. Abacavir is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in *HLA-B*57:01*-positive patients	[128]
	*-B*57:01*	EMA	Before initiating treatment with abacavir, screening for carriage of the *HLA-B*57:01* allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the *HLA-B*57:01* allele	[129]
	*-B*57:01*	CPIC	*HLA-B*57:01* screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy. In abacavir-naive individuals who are *HLA-B*57:01*-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk	[122, 123]
Allopurinol	*-B*58:01*	EMA	The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. Routine testing for *HLA-B*5801* is not recommended in any patient. If the patient is a known carrier of *HLA-B*58:01*, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required, and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms	[130]
	*-B*58:01*	CPIC	Allopurinol is contraindicated in patients who are carriers of *HLA-B*5801* (*HLA-B*5801/*X*, *HLA-B*5801/HLA-B*5801*)	[124, 125]
Carbamazepine	*-B*15:02*	FDA	Prior to initiating carbamazepine therapy, testing for *HLA-B*15:02* should be performed in patients with ancestry in populations in which *HLA-B*1502* may be present. Carbamazepine should not be used in patients positive for *HLA-B*15:02* unless the benefits clearly outweigh the risks	[128]
	*-A*31:01*	FDA	The risks and benefits of Tegretol therapy should be weighed before considering administering Tegretol in patients known to be positive for *HLA-A*31:01*	[128]
	*-B*15:02*	EMA	Individuals of Han Chinese and Thai origin should, whenever possible, be tested for the *HLA-B*15:02* allele prior to treatment with carbamazepine. Testing for the *HLA-B*15:02* allele in other Asian populations at genetic risk may be considered	[130]
	*-A*31:01*	EMA	Routine testing for the *HLA-A*31:01* allele is not recommended. If European Caucasians or patients of Japanese descent are known to be positive for the *HLA-A*31:01* allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks	[130]
	*-B*15:02*	CPIC	Regardless of the individual's ancestry or age, if the genetic testing results are "positive" for the presence of at least one copy of the *HLA-B*15:02* allele, it is recommended that a different agent be employed depending on the underlying disease, unless the benefits clearly outweigh the risk	[127]
Phenytoin	*-B*15:02*	FDA	Consideration should be given to avoid phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*15:02*	[128]
	*-B*15:02*	CPIC	Regardless of the *CYP2C9* genotype and individual's ancestry or age, if the *HLA-B*15:02* test result is "positive", the recommendation is to consider administering an anticonvulsant other than carbamazepine and phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks. Alternative medications such as oxcarbazepine, eslicarbazepine acetate and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele; thus, caution should be exercised in choosing alternatives to phenytoin	[126]

CPIC, clinical pharmacogenetics implementation consortium; FDA, food and drug administration; EMA, European medicine agency; HLA, human leukocyte antigen. [a]This information is part of the text included as a recommendation in published articles and labeling information of each drug

regimen, individualizing the regimen, increasing efficacy and avoiding ADRs [131]; thus, the implementation of pharmacogenomics in routine practice can improve different drug treatments [132].

Pharmacogenetic testing is also of relevance for the economic resources of the patient or the public health system. Several studies have demonstrated that *HLA* testing prior to various drug prescriptions is cost-effective but that this also depends on the population to which it will be applied. For instance, *HLA-B*15:02* genotyping prior to CBZ prescription is cost-effective for Singaporean Chinese, Malays and Thai patients [133, 134] but not for Singaporean Indians [133]. For Europeans, a study reports that testing for *HLA-A*31:01* represents a cost-effective use prior to initiation of CBZ therapy [135]. Contrariwise, testing for *HLA-B*58:01* did not represent a benefit in allopurinol therapy in Singaporean patients, in contrast with the profit observed in Thai and Korean populations [71, 136]. *HLA-B*57:01* screening prior to abacavir was found to be cost-effective for patients from Spain and Germany [137, 138]. However, a systematic review found that there is cost-effectiveness in the use of pharmacogenetic biomarkers to avoid ADRs in common drug therapies [139].

On the other hand, several investigations have been performed in order to develop assays that reduce the cost of *HLA* screening, i.e. nested allele-specific PCR and PCR-RFLP for *HLA-A*31:01* detection [140, 141], flow cytometry pre-screening [142], real-time PCR [143] for *HLA-B*57:01* and the flow cytometry test for *HLA-B*58:01* [144]. Furthermore, the search for single-nucleotide polymorphisms in linkage disequilibrium with specific *HLA* alleles could diminish the cost of *HLA* genotyping and make it more available for different populations [145, 146].

However, there are some limitations for *HLA* genotyping in cases of rare ADRs that should be taken into account. In general, the incidence of ADRs associated with *HLA* alleles is low; for instance, allopurinol hypersensitivity has been reported in 0.1% [147], and it represents a problem in association studies. This explains the small sample size observed in the majority of studies, which limits the study power for detecting significant associations [148]; however, meta-analyses can help solve this problem, especially in populations that are widely studied. In addition, investigations employing a scarce number of patients could lead to many associated *HLA* alleles, in which further studies are required in order to confirm their use as pharmacogenetic biomarkers. This situation could impact the cost-effectiveness of *HLA* typing prior to drug prescription in uncommon ADRs [149].

In sum, several *HLA* alleles have been associated with ADRs to common drugs; however, the strongest associations remain for *HLA-B*58:01*, *HLA-B*57:01*, *HLA-B*15:02* and *HLA-A*31:01*, but only in certain populations. In addition, the majority of the studies have been performed in Asians and Caucasians, and there is a lack of reports on other populations. This situation renders it difficult for international medicine agencies to offer global recommendations on *HLA* genotyping prior to drug prescription or for their including more populations in their warnings. Moreover, it might be possible that more *HLA* alleles are associated with ADRs in other, not yet studied ethnic groups; therefore, pharmacogenomic investigations on this issue should not be pushed aside. The existence of *HLA* allele databases that facilitate these studies and the reports that assure the cost-effectiveness of *HLA* screening could ease pharmacogenomic research of ADRs focused on *HLA* alleles.

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