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Review

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Pharmacogenomics

HLA pharmacogenetic markers of drug hypersensitivity from the perspective of the populations of the Greater Middle East

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Specific HLA associations with drug hypersensitivity may vary between geographic regions and ethnic groups. There are little to no data related to HLA-drug hypersensitivity on populations who reside in the Greater Middle East (GME), a vast region spanning from Morocco in the west to Pakistan in the east. In this review, the authors intended to summarize the significant HLA alleles associated with hypersensitive drug reactions induced by different drugs, as have been found in different populations, and to summarize the prevalence of these alleles in the specific and diverse populations of the GME. For example, *HLA-B*57:01* allele prevalence, associated with abacavir-induced hypersensitivity, ranges from 1% to 3%, and *HLA-DPB1*03:01* prevalence, associated with aspirin-induced asthma, ranges from 10% to 14% in the GME population. Studying pharmacogenomic associations in the ethnic groups of the GME may allow the discovery of new associations, confirm ones found with a low evidence rate and enable cost–effectiveness analysis of allele screening before drug use.

Tweetable abstract: What is known about HLA alleles and drug hypersensitivity associations in the populations of North Africa and the Middle East and the potentiality of genomic tools and projects to propose possible opportunities.

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Keywords: adverse drug reactions • drug hypersensitivity • Greater Middle East • HLA pharmacogenomic associations • HLA polymorphism

In a global concerted effort toward personalizing medicine using genome information, pharmacogenomics has become mainstream. It is the discipline of studying an individual's genetic characteristics underlying drug efficacy or adverse drug reactions. Adverse drug reactions (ADRs) are defined by the WHO as:

"*a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function*" [1].

ADRs are broadly classified as type A reactions (augmented pharmacologic effects) or type B reactions (bizarre or idiosyncratic reactions). Type A ADRs are predictable, dose dependent and related to the pharmacologic activity of the drug (e.g., bleeding related to the anticoagulant warfarin), whereas type B ADRs, also known as hypersensitive drug reactions (HDRs) or idiosyncratic adverse drug reactions, are not an extension of the drug's pharmacologic effect are generally dose independent unpredictable and result from interactions between a pharmacologic agent and the human immune system (e.g., abacavir hypersensitivity or anaphylaxis to penicillin) [1–3]. Studies have reported variable percentages of hospitalization related to the different types of ADRs, ranging from 3.5% to 15%, based on studies conducted in Europe and the USA [4,5]. Along with morbidity and mortality, ADRs represent a financial

burden to healthcare providers, as they are associated with prolonged length of stay and subsequent increase in the cost of hospitalization [4,5]. ADRs also confer a financial burden on the pharmaceutical industry as a leading cause of drug withdrawal from the market [6].

Although type B reactions account for only 15–30% of ADRs, they present more severe reactions than type A reactions, leading to significant morbidity, mortality and socioeconomic burden [3]. The most common HDRs include cutaneous adverse drug reactions. Examples of life-threatening severe cutaneous adverse reactions include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reactions with eosinophilia and systemic symptoms (DRESS).

For over 30 years, multiple reports have shown that life-threatening HDRs are associated with specific alleles of the HLAs on the short arm of chromosome 6, considering their role in peptide presentation in the adaptive immune response. The genes within the human MHC – in particular, those that encode the MHC class I and MHC class II – that are highly polymorphic, [7,8] and variants potentially code isoforms that may modulate the response. Alternatively, since the genes of the MHC are in tight linkage disequilibrium [7], candidates within specific haplotypes may be involved. The carriage rate of HLA alleles differs among populations and across different geographic areas [9]. Infectious agents and epidemics in the world regions may have played a main role in the selective pressure behind HLA polymorphism and variability across the globe. Therefore, it is not surprising that HLA-ADR association reports have varied in different populations [10].

Several HLA alleles have been proposed as valid genetic markers for preventing life-threatening reactions, mainly in Asian and Western populations, where studies have confirmed HLA-HDR associations [11–13]. By establishing these markers, it may be possible to avoid some drug-induced immune reactions. For not yet well-studied populations, information about the frequencies of these pharmacogenetic HLA alleles, robustly involved in hypersensitive reactions, may present a first step toward associations to be studied in a specific population. Association studies should then be conducted in the specific population to confirm the HLA allele-HDR association and to determine the relative positive and negative predictive value of HLA allele screening before drug use. Consequently, cost–effectiveness or the cost–utility analysis, based on determined predictive values in a specific population, would address the clinical implementation of allele screening tests.

In this regard, this review summarizes the frequencies of HLA alleles, strongly associated with ADRs, in the different populations of the Greater Middle East (GME) and discusses the potentiality of using HLA alleles as pharmacogenetic markers of drug hypersensitivity from the perspective of the populations of the GME.

Immunopathogenesis of HLA-mediated hypersensitivity drug reactions

The HLA class I (*HLA-A, -C* and *-B*) and class II (*HLA-DRA1, HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DP1* and *HLA-DPB1*) genes encode the MHC class I and class II proteins, respectively. Those cell surface proteins regulate the immune response by distinguishing the body's own proteins (self) from foreign proteins (nonself) through peptides presentations. HLA genes are known to be highly polymorphic within and across human populations. This polymorphism accounts for the diversity in protein variant, especially within the peptide-binding groove that subsequently controls the adaptive immune system interaction.

Drug molecules and reactive metabolites could result in subsequent T-cell-mediated immune reactivity involving HLA molecule antigen presentation. In some cases, the interaction between the patient's specific MHC molecules and the drug molecules can induce ADRs through $CD8^+$ (MHC class I) and/or $CD4^+$ (MHC class II) T-cell-mediated reactions, even though the precise mechanisms at the molecular level of HLA–drug interactions are still poorly understood [14,15].

Three main models potentially explain the immune-pathogenesis of ADRs with human MHC molecules: the hapten/prohapten model, the altered peptide repertoire model and the pharmacologic interaction model (Figure 1) [13].

In the hapten/prohapten model, the ADR results from covalent binding of the drug to an endogenous cell-protein, forming a complex of drug-haptenized peptide, presented then at the cell surface by the MHC molecule. The drug–protein complex is then recognized by T-cell receptors on T cells and initiates the innate immune system [16]. In the altered peptide repertoire model, the HDR results from noncovalent binding of the drug and a self-peptide or a drug-induced self-peptide with MHC molecules recognized therefore as foreign by T cells [17]. In the pharmacologic interaction model, the HDR results from a noncovalent interaction between the drug molecules and HLA, creating neoantigens, which will result in a T-cell-mediated immune reaction [18].

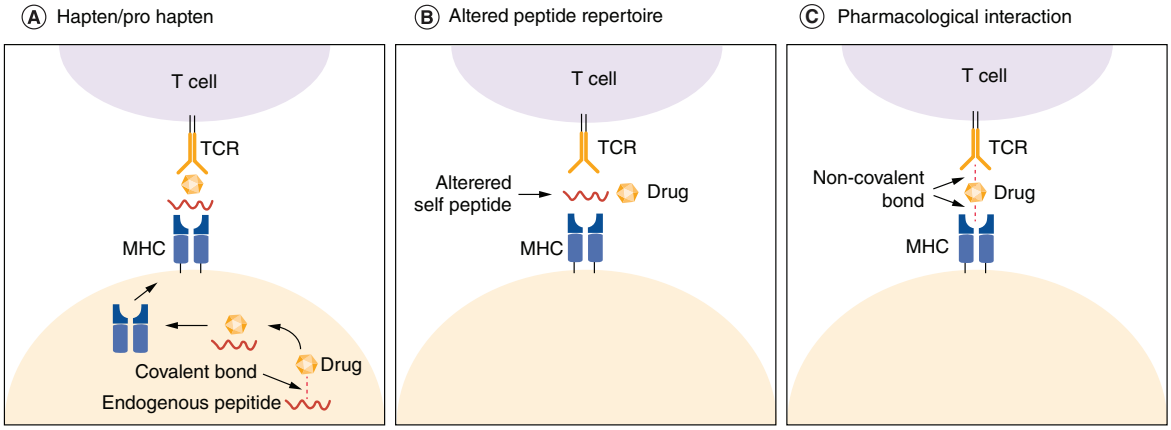

Figure 1. Immunopathogenic models of MHC adverse drug reactions. (A) Hapten/prohapten model: adverse drug reactions are caused by a drug metabolite forming a covalent bond with an endogenous protein, which is then presented by the MHC. **(B)** Altered protein repertoire model: the drug molecule noncovalently binds with an altered self-peptide to the MHC, causing a change in its binding cleft, causing T cells to recognize the peptide as foreign. **(C)** Pharmacologic interaction model: the drug molecule forms a noncovalent bond directly with the T-cell receptor or the MHCs, which results in T-cell activation.
TCR: T-cell receptor.

Abacavir and *HLA-B*57:01* is an example of a well-established HLA-HDR association exceptionally well studied at the molecular/mechanistic level. Abacavir binds noncovalently to the *HLA-B*57:01* peptide-binding cleft, thereby causing conformational changes in the self-peptide-binding motif and inducing a primary immune response, as per the altered peptide repertoire model [19].

Frequencies of HLA alleles involved in pharmacogenomic associations among the GME populations

The complete list of pharmacogenomic associations involving HLA alleles is regularly updated and available on the Pharmacogenomics Knowledge Base website with assigned ratings indicating their 'strength of evidence' (www.pharmgkb.org/) [20]. Well-characterized pharmacogenomic associations were extracted from the Pharmacogenomics Knowledge Base; only associations with clinical annotations and levels of evidence from 1 to 2, considered as associations with moderate/robust data, were considered for the genes of HLA class I (*HLA-A, -C* and *-B*) and HLA class II (*HLA-DRB1, HLA-DQA1* and *HLA-DPB1*) (Figure 2).

The authors reviewed the prevalence of these alleles in different populations of the GME (Table 1). High-resolution genotyping to determine the frequencies of different HLA alleles have been completed by previous studies for different populations in the GME, including HLA alleles reported to be involved in HLA-HDR associations. Closely related alleles, not discriminated by two-field typing, may have a completely different impact over a specific adverse reaction. Therefore, the authors reported only allele frequencies of HLA alleles determined with two-field high-resolution HLA genotyping. Table 1 summarizes the prevalence of HLA alleles, class I (*HLA-A, HLA-C* and *HLA-B*) and class II (*HLA-DP, HLA-DR* and *HLA-DQ*), involved in well-characterized pharmacogenomic associations, as determined in the different populations of the GME [74]. For HLA allele frequencies in the populations of the GME, the authors referred to the HLA allele frequencies database [9], systematic reviews and published peer-reviewed articles, as inserted in the table within each reported frequency.

Cutaneous adverse reactions, DRESS or TEN syndromes have been recurrently reported as drug reactions after allopurinol and antiepileptic drug treatment in Moroccan, Tunisian, Iranian and Emiratis patients [21–26]. However, a limited number of studies have addressed HLA-HDR associations in the region. A case–control study showed a significant association between *HLA-A*31:01* allele and DRESS induced by carbamazepine in a Tunisian cohort [27]. Associations between *HLA-DQB1*03:02* and *HLA-DRB1*04* and aspirin-exacerbated respiratory disease, as well as the study of *HLA-B*57:01*-abacavir hypersensitivity reaction in a small cohort, have been reported from Iran [28,29]. The limited number of studies (based on thorough research in PubMed and Google Scholar, combining different keywords such as MHC, HLA, drug and hypersensitivity and names of populations and countries) contrasts with the diversity and the distinctiveness of populations in the region. Gene candidate studies or genome-wide association

Table 1. A. Frequency of known HLA allele associations with drug hypersensitivity in the populations of the Greater Middle East.

Drug	Allele frequency, % (sample size)								Ref.
	PharmGKB level of evidence	HLA allele	Adverse drug reaction(s)	Northwest Africa	Northeast Africa	Levant	Arabian Peninsula	Pakistan and Persia	
Abacavir	1A	*B*57:01*	Drug hypersensitivity, DRESS	TUN: 3% (100)	SUD: 1.5% (200)	JOR: 1% (146)	SAU: 1.43% (105)	IRAN-Bal: 1% (100)	[68,71,76,77]
				LYB: 0.8% (118)			UAE-Abu D: 0.9% (52)		[70,76]
				Mor-ch: 2.7% (98)					[78]
Carbamazepine Phenytoin Oxcarbazepine sulfamethoxazole/ trimethoprim	1A	*B*15:02*	SJS, TEN	No data or research	No data or research	No data or research	UAE: 0.6% (373)	No data or research	[76]
							UAE-Abu D: 0.9% (52)		[76]
Carbamazepine	1A	*A*31:01*	DRESS, MPE, SJS, TEN	TUN: 0.4% (376)	SUD: 3% (200)	JOR: 1.7% (146)	SAU: 4.11% (105)	IRAN-Bal: 2.2% (100)	[68,71,76,77,79]
				LYB: 5% (118)			UAE-Abu D: 2.8% (52)	PAK-BAL: 0.8% (66)	[70,76]
				Mor-ch: 2% (98)			OMAN: 2.5% (118)	Pak-Sindhi: 4.4% (101)	[76,78]
Carbamazepine	2A	*B*15:11*	SJS, TEN	No data or research	No data or research	No data or research	No data or research	No data or research	
Carbamazepine	2A	*B*40:01*	SJS, TEN	TUN: 1.5% (100) LYB: 0.8% (118) Mor-ch: 1.4% (98)	SUD: 1% (200)	JOR: 0.3% (146)	Saudi: 0.3% (105) UAE: 0.6% (373)	No data or research	[68,70,71,76,78,80]

PharmGKB levels of evidence for clinical annotations. The table includes only associations with levels of evidence from 1 to 2, considered as associations with robust data to moderate evidence of an association, as per the PharmGKB. Only one association with a level of evidence 3 has been included, as it was reported as a US FDA pharmacogenomic biomarker in drug labeling. When there is no mention of the frequency of one population, it means that no studies were found reporting the prevalence in this population.

ALG: Algerians; BAH: Bahraini; DRESS: Drug reaction with eosinophilia and systemic symptoms; EGY: Egyptian; IRAN-Bal: Iranian-Baloch; JOR: Jordanian; KWA: Kuwaiti; LEB: Lebanese; LYB: Lybian; LYB-Jews: Lybian Jewish; MPE: Maculopapular exanthema; MOR: Moroccan; Mor-ch: Moroccan Chaouya; OMAN: Omani; PAK-BAL: Pakistan-Baloch; Pak-Sindhi: Pakistan-Sindhi; PAL: Palestinian; PharmGKB: Pharmacogenomics Knowledge Base; SAU: Saudi; SJS: Stevens–Johnson syndrome; SUD: Sudanese; TEN: Toxic epidermal necrolysis; TUN: Tunisian; UAE: Emiratis; UAE-Abu D: Emiratis Abu Dhabi; YEM-Jews: Yemenite-Jews.

Table 1. A. Frequency of known HLA allele associations with drug hypersensitivity in the populations of the Greater Middle East (cont.).

B. Frequency of known HLA allele associations with drug hypersensitivity in the populations of the Greater Middle East.

Allopurinol	1A	*B*58:01*	SJS, DRESS, TEN	TUN: 2% (376) LYB: 3.3% (118) Mor-ch: 3.4% (98)	SUD: 4.5% (200)	JOR: 1.3% (146)	UAE-Abu D: 4.8% (52)	IRAN-Bal: 4% (100)	[70,71,76–79]
Allopurinol	2B	*A*33:03*	Drug hypersensitivity, SJS	TUN: 5% (100)	SUD: 2.5% (200)	No data	SAU: 3.48% (105)	IRAN-Bal: 5.6% (100)	[68,76,77,80]
				LYB: 3.3% (115)			UAE- Abu D: 4.8% (52)	PAK-bal: 12.7% (66)	[9,70,76]
				Mor-ch: 1.4% (98)			OMAN: 2.1% (118)	Pak-Sindhi: 7.6% (101)	[76,78]
Allopurinol	2B	*C*03:02*	SJS, TEN	TUN: 1% (100)	SUD: 0.5% (200)	JOR: 6% (146)	SAU: 1.5% (105) UAE-Abu D: 4.8% (52)	IRAN-Bal: 4.7% (100)	[68,71,76,77]
Sulfamethoxazole/ trimethoprim	2A	*B*38:02*	SJS, TEN	No data	No data	No data	No data	No data	
Dapsone sulfamethoxazole/ trimethoprim	2A	*B*13:01*	Drug hypersensitivity, DRESS, SJS, TEN	TUN: 0.1% (376)	SUD: 0% (200)	No data	No data	No data	[76,79]
Methazolamide	2A	*B*59:01*	SJS, TEN	No data	No data	No data	No data	No data	
Methazolamide	2B	*C*01:02*	SJS, TEN	No data	No data	No data	UAE-Abu D: 4.8% (52)	IRAN-Bal: 4.7% (100)	[76,77]
Aspirin	2B	*DPB1*03:01*	Asthma	TUN: 13.9% (100)	SUD: 10.5% (200)	No data	No data	No data	[76,80]

PharmGKB levels of evidence for clinical annotations. The table includes only associations with levels of evidence from 1 to 2, considered as associations with robust data to moderate evidence of an association, as per the PharmGKB. Only one association with a level of evidence 3 has been included, as it was reported as a US FDA pharmacogenomic biomarker in drug labeling. When there is no mention of the frequency of one population, it means that no studies were found reporting the prevalence in this population.

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Table 1. A. Frequency of known HLA allele associations with drug hypersensitivity in the populations of the Greater Middle East (cont.).

C. Frequency of known HLA allele associations with drug hypersensitivity in the populations of the Greater Middle East.									
Lapatinib	3	*DRB1*07:01*	Drug-induced liver injury	LYB: 17% (118) LYB-Jews: 19% (119) ALG: 13-16% (100–97) TUN: 19%, 20% (376, 100) MOR: 12.3% (96) Mor-ch: 16% (98)	EGY: 9% (121) SUD: 7.8% (200)	JOR: 26.9% (146) LEB: 6.3%, 8.8% (95, 563) PAL: 12.7% (109)	SAU: 26.6% (105) BAH: 9% (72) UAE-Abu D: 14.4% (52) YEM-Jews: 22.1% (76)	IRAN: 9.1% (100) IRAN-Bal: 3% (100)	[68–72,76–83]
Lapatinib	2B	*DQA1*02:01*	Drug-induced liver injury	ALG: 12.25% (106) TUN: 17.2% (100) MOR: 12.6% (96) Mor-ch: 18% (98)	No data	JOR: 26.9% (146) PAL: 12.8% (109)	KWA: 10.7% (78) YEM-Jews: 22.1% (76)	IRAN-Bal: 3.5% (100) Iran: 21.6% (58)	[71,76–78,80–82,84]
Nevirapine	2A	*B*35:01*	Drug hypersensitivity	TUN: 4.8% (100)	SUD: 4.3% (200)	JOR: 0.3% (146)	UAE-Abu D: 3.8% (52)	IRAN-Bal: 8.1% (100)	[71,76,77,80]
				Mor-ch: 3.4% (98)					[78]
Nevirapine	2B	*C*04:01*	DRESS, SJS, TEN	TUN: 11.6% (100) Mor-ch: 12% (98)	SUD: 13.5% (200)	JOR: 10% (146)	BAH: 14.9% (72) SAU: 7.9% (105) UAE-Abu D: 14.4% (52)	IRAN: 15.4% (120) IRAN-Bal: 28.6% (100)	[68,71,72,76–78]
Nevirapine	2B	*DRB1*01:01*	Drug hypersensitivity	ALG: 1.5% (100) TUN: 0.6-2% (376–100) LYB: 0.4% (118) MOR: 2% (96) Mor-ch: 1% (98)	EGY: 0% (121) SUD: 0% (200)	JOR: 3.8% (146) LEB: 5.8% (95) PAL: 2.3% (109)	BAH: 1.4% (72) SAU: 0.6% (105) UAE-Abu D: 0.9% (52) YEM-Jews: 1.3% (76)	Iran: 5.5% (100) IRAN-Bal: 15% (100)	[68,70–72,76–83]

PharmGKB levels of evidence for clinical annotations. The table includes only associations with levels of evidence from 1 to 2, considered as associations with robust data to moderate evidence of an association, as per the PharmGKB. Only one association with a level of evidence 3 has been included, as it was reported as a US FDA pharmacogenomic biomarker in drug labeling. When there is no mention of the frequency of one population, it means that no studies were found reporting the prevalence in this population.

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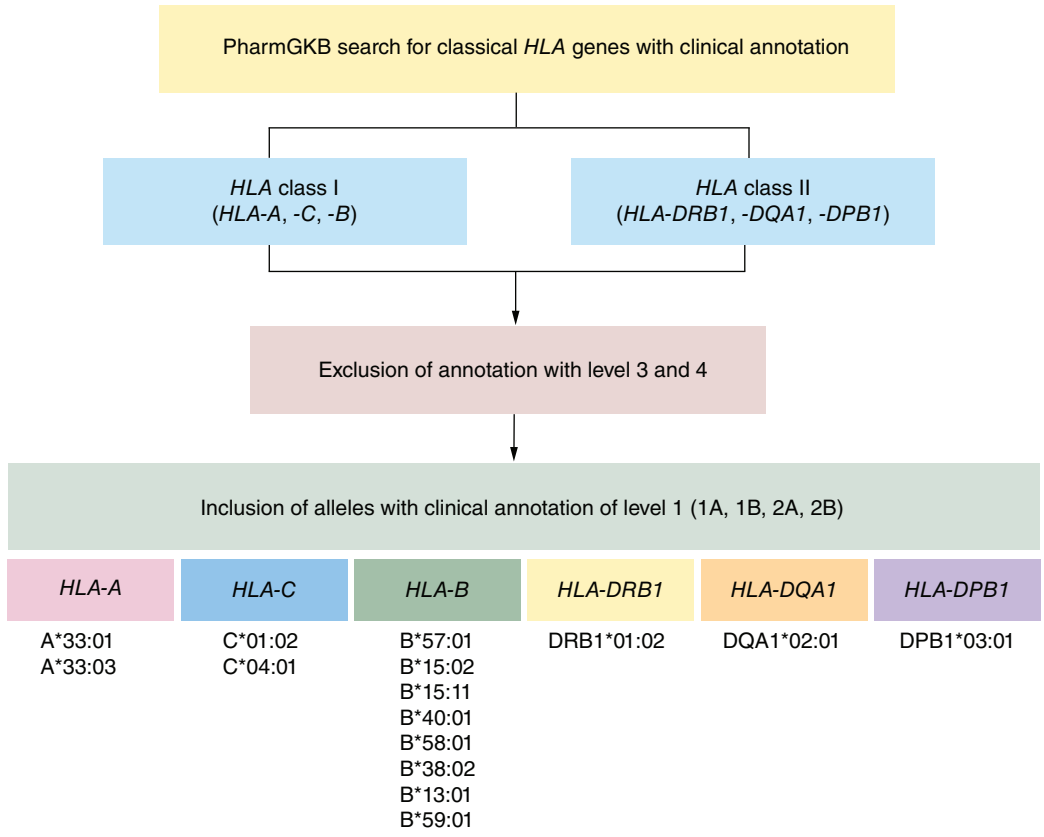

Figure 2. Search methodology used in this review to extract HLA alleles with pharmacogenomic associations from the Pharmacogenomics Knowledge Base website with assigned ratings indicating their 'strength of evidence' level. Only associations with clinical annotations and levels of evidence from 1 to 2, considered as associations with moderate/robust data, were considered for the genes of HLA class I (*HLA-A, -C* and *-B*) and HLA class II (*HLA-DRB1, HLA-DQA1* and *HLA-DPB1*).

studies (GWAS), in GME populations, may identify new associations, or confirm known HLA associations in the populations of the GME.

Along with the allele prevalence in one population, several other factors are considered when HLA allele genotyping is to translate into clinical routine. Among these factors are the frequency, the severity of the drug-induced reaction, the positive-predictive value (PPV) and negative-predictive value (NPV) of the HLA allele screening test and the number of patients needed to be tested to prevent one case of hypersensitive reactions (HSRs). These factors provide information about the efficiency of HLA screening tests in preventing drug reactions and addressing the cost–effectiveness aspect in a specific population.

HLA carrier frequency is correlated with the prevalence of associated HDRs in the relative population and therefore may provide a rough guide to the associations that need to be studied in the GME populations. However, case–control studies are needed to confirm any HLA-HDR association and to define the PPV and the NPV of the specific allele screening, to address the cost–effectiveness of clinical test screening implementation in the respective population. The PPV is informing about the extent of additional risk factors, other genetic loci or environmental factors that may intervene to induce ADRs in patients carrying the HLA allele, and the NPV is informing about the probability of hypersensitivity reaction based on the absence of HLA allele. Thereafter, the PPV and the NPV are indispensably required as input parameters to study the cost–effectiveness of an allele screening test in a population, and they are more informative of the clinical utility of a screening testing than the allele frequency [30].

Abacavir & HLA-associated hypersensitivity

Abacavir is a nucleoside reverse transcriptase inhibitor used in the treatment of HIV infection. Abacavir-induced hypersensitivity includes fever, generalized rash, fatigue, gastrointestinal symptoms and shortness of breath. *HLA-*

*B*57:01* is associated with abacavir-induced hypersensitivity. Several independent studies have found abacavir hypersensitivity and *HLA-B*57:01* association in North Americans [31], Western Australians [32] and Europeans [33,34]. The PREDICT-1 study, a double-blind, prospective, randomized study including 1956 HIV-infected patients from 19 countries, confirmed the sensitivity of *HLA-B*57:01* as a marker for screening to prevent abacavir hypersensitivity, with an NPV of 100% [33]. However, 82% of the enrolled patients were Caucasians. Later on, the sensitivity of *HLA-B*57:01* as a marker of abacavir hypersensitivity was found in African–American patients with immunologically confirmed (skin patch) abacavir hypersensitive reaction [35]. Screening for *HLA-B*57:01* should be completed prior to abacavir treatment, as warned on the FDA's box label, by the EMA [33] and by Clinical Pharmacogenetics Implementation Consortium guidelines [36].

The prevalence of the *HLA-B*57:01* allele, associated with abacavir-induced hypersensitivity, ranges from 1% to 3% in the GME populations. *HLA-B*57:01* has been found to be associated with abacavir hypersensitivity in Caucasians, African–Americans and Thai populations, where the prevalence of the allele is approximately 6%, 2% and 4%, respectively. In Chinese and Koreans, the prevalence of the allele is 0.8% or lower, justifying their questioning the benefit of *HLA-B*57:01* screening, upon guidelines recommendations, in their relative countries [37]. A very few cases of hypersensitivity to abacavir are detected within a large cohort of HIV patients in these countries, which did not decrease even after introducing HLA-B*57:01 screening [38]. From the authors' point of view, associations involving HLA-B*57:01 deserve to be studied in at least the population of North Africa, as they are about 3% carriers of the allele, to address the clinical implementation of screening tests before drug use, complying with the FDA drug warning.

Carbamazepine & HLA-associated hypersensitivity

Carbamazepine is an anticonvulsant that is used to prevent and control seizures. HLA alleles with B75 serotypes, *HLA-B*15:02* and *HLA-B*15:11* are predisposing alleles to carbamazepine adverse cutaneous reactions, SJS, TEN, maculopapular exanthema and DRESS; only Asian populations were found to be a carrier of these alleles, explaining the FDA statement that their screening before treatment is to be completed in carrier populations or patients with southeast Asian ancestry. *HLA-B*15:02*'s strong association with SJS/TEN caused by carbamazepine was reported first in Han Chinese patients; the study found that 100% SJS patients group carried *HLA-B*15:02,* whereas only 3% carried the allele in the tolerant patient group [39]. The association has been confirmed in different Asian populations, including Chinese, Thai, Korean, Malay, Vietnamese and Indian populations [40–45]. Other populations, such as Japanese and Caucasians, are low or null carriers of the *HLA-B*15:02* allele, which explains the difficulty of replicating the association in these populations [46,47]. Indeed, the frequency of *HLA-B*15:02* is higher in southeast Asians than in Caucasians and Japanese (2–8% vs <0.1%) [32].

GME populations are not or are lower carriers of these alleles, as they have been rarely reported by studies achieved in these populations. However, the prevalence of another allele associated with carbamazepine cutaneous adverse reaction, *HLA-A*31:01*, associated with HDRs in Caucasians and Asians [47–49], may range from 0.5% to 5% in the GME and may predispose these populations to carbamazepine cutaneous adverse reactions. In Tunisians, one study found a significant association between *HLA-A*31:01* and carbamazepine HDRs [27], confirmed by a study in a larger cohort. More studies are required to assess the significant association and to determine the predictive value of *HLA-A*31:01* screening in the GME populations in preventing carbamazepine hypersensitivity. The association is warned on the FDA drug label and its screening in patients of all ancestries is recommended by the Canadian Pharmacogenomics Network for Drug Safety and the Canadian Department for National Public Health (Health Canada – Santé Canada) [48,50]. It is worth noting that the *HLA-A*02:01* allele, reported in association with increased risk of maculopapular exanthema induced by carbamazepine and lamotrigine treatment [49,51], has a prevalence of 17–20% in North African and Middle Eastern populations [52]. This association is not reported in Table 1, as the related strength of evidence is level 3 and therefore considered an association with a low level of evidence in the Pharmacogenomics Knowledge Base.

Allopurinol & HLA-associated hypersensitivity

Several alleles have been found to predispose patients to allopurinol-induced SJS and TEN syndromes: *HLA-B*58:01, HLA-A*33:03* and *HLA-C*03:02*. Allopurinol is a xanthine oxidase inhibitor used in the first-line treatment of gout and hyperuricemia.

A strong association between *HLA-B*58:01*/allopurinol-mediated severe cutaneous adverse reactions, SJS, TEN and DRESS was found in different populations: Han Chinese, Thais and Koreans [43,53–57]. A weaker but significant

association was also found in Japanese and Europeans, where the *HLA-B*58:01* allele frequency is lower (example: 20% in Han Chinese vs 1–5% in Europeans) [58,59].

The prevalence of *HLA-B*58:01* in the GME populations may range from 2% to 5% in North Africans and Middle Easterners, and 4–5% in those in the Arabic Peninsula and Persians. The Clinical Pharmacogenetics Implementation Consortium recommends not prescribing allopurinol to patients positive for *HLA-B*58:01* and that negative genotype does not exclude the possibility of HDRs, especially in Europeans [60]. The incidence of severe cutaneous adverse reactions in the Taiwanese population significantly decreased in patients positive for *HLA-B*58:01* when allopurinol was stopped and an alternative treatment was used [61].

Another HLA allele associated with allopurinol HDRs is *HLA-A*33:03*, found significantly in Europeans [62]. *HLA-A*33:03* in Pakistani populations is reaching 7–12%, which should certainly motivate studying the association in allopurinol HDR patients.

Nevirapine & HLA drug-associated hypersensitivity

In one study, *HLA-C*04:01* was significantly associated with an increased risk of developing cutaneous adverse reactions and hepatotoxicity hypersensitivity to nevirapine, an antiretroviral therapy. This association was found to be significant in a number of different ethnic populations: Black Africans, Caucasians and Thais. Its frequency may range from 8% to 14% in the GME populations or even higher in the Iranian-Baloch population, where it may reach 28%. *HLA-B*35:01* and *HLA-DRB1*01:01* are also associated with nevirapine hypersensitivity and populations of the GME are carriers of these alleles. As *HLA-C*04:01*, *HLA-B*35:01* and *HLA-DRB1*01:01* are in linkage disequilibrium, reported associations could be haplotype dependent rather than allele dependent [63].

Lapatinib & HLA-associated hepatotoxicity

Lapatinib is a tyrosine kinase inhibitor used in combination therapy for advanced or metastatic HER2-positive breast cancer. *HLA-DRB1*07:01* carriage is significantly associated with serum alanine aminotransferase elevation in lapatinib-treated patients. These HLA alleles are present in approximately 15–25% of Caucasian, Asian, African and Hispanic populations and 1% in Japanese populations. Their prevalence may range from 10% to 25 % in the GME. The FDA statement on the lapatinib drug label is that liver function should be monitored in all patients receiving lapatinib therapy, regardless of genotype.

Aspirin & HLA-associated asthma

*HLA-DPB1*03:01* is carried by ~10% and 14% of Sudanese people and Tunisians, respectively, and has been strongly associated with aspirin-induced asthma in asthmatic patients. The association has been found in the White Polish population and Koreans, and further studies will be needed to replicate the finding in different populations and to investigate other HLA alleles in linkage disequilibrium with the *HLA-DPB1*03:01* allele [64,65].

Cost–effectiveness of HLA screening prior to drug use

Cost–effectiveness analysis and health technology assessment aim to achieve better health in ways that the introduced testing is affordable and acceptable. They evaluate health outcomes relative to monetized input, for better and efficient allocations of resources in healthcare settings. Different studies have evaluated the cost–effectiveness of screening HLA alleles robustly associated with HSR in different countries. For example, the cost–effectiveness analysis of *HLA-B*57:01* screening prior to abacavir use was done in the USA [66] and in the UK [34]. An incremental cost–effectiveness ratio of the *HLA-B*57:01* screening test was evaluated at $36,700/quality-adjusted life year when compared with no testing in the USA, and €22.811 per hypersensitivity reaction avoided in the UK. Based on the results of these studies, the *HLA-B*57:01* screening test was considered cost effective for the relative countries, considering the prevalence, the PPV, the NPV and the threshold of cost–effectiveness relative to the USA and UK. In Indonesia, the screening of *HLA-B*15:02* prior to carbamazepine treatment was evaluated and found not to be cost effective [67]. Along with the allele prevalence in one population, the PPV and the NPV are indispensably required as input parameters to study the cost–effectiveness of an allele screening test in a population; this should motivate more studies in the GME populations in the particular case of HLA presenting high variability across ethnicities.

Conclusion

We summarized the frequency of significant HLA alleles associated with HDRs induced by different drugs reported mainly by studying Western and Asian populations, in different populations of the GME. Regarding the lack of studies of association from the GME populations, our review intended to motivate researchers to undertake gene candidate studies or GWASs in these populations. We underscore the need to study associations with HLA alleles presenting high prevalence, such as *HLA-A*33:03*, associated with allopurinol HDRs (12.7% in Pakistan); *HLA-DPB1*03:01*, associated with aspirin-induced asthma in North Africa (13.9%); and *HLA-A*31:01*, associated with carbamazepine in North Africa, where the prevalence may reach 5%. We mentioned that *HLA-A*02:01* has been associated with the increased risk of maculopapular exanthema induced by carbamazepine and lamotrigine; the association should be studied in the GME populations where the prevalence ranges from 17 to 20% to be confirmed. Gene candidate studies or GWASs, in GME populations, may discover new associations or confirm associations with a low level of evidence involving HLA alleles carried more frequently in the populations of the GME than in other populations. The advent of next-generation sequencing (NGS), a high-throughput sequencing technique, has brought many advancements to HLA profiling, providing higher resolution of HLA genotyping. The scalability of NGS and the various bioinformatic tools that have been developed to achieve HLA genotyping provide an interesting opportunity to reduce the knowledge gap in the characterization of HLA-HDR associations in the GME populations. Among the studies that we referred to in our review, HLA genotyping to determine HLA allele frequencies has conducted by NGS in Saudi Arabians [68], while it has been conducted using sequence-specific oligonucleotide probes or sequence specific primer for most of the different other studies on the GME populations [69–72]. In Middle East/North African countries, HLA genotyping with NGS has been used for other applications – for example, to study allele association to severe COVID-19 infection in the UAE [73].

Despite a considerable number of discovered HLA allele associations, the transition into clinical practice has been made only for a few, well-characterized associations. Many challenges, such as the rarity of hypersensitivity reactions and the high ethnic variability over the world, slow down the pace of the progress. Discovering new associations by studying GME populations could improve the outcome of patients belonging to these populations and overall may improve the efficiency of screening by tagging HLA alleles of different ethnicities associated with ADRs [75]. Consortium efforts and clinical networks with the largest involvement of professionals from the GME region would advance discoveries and would have a clinical impact on avoiding severe drug reactions.

Future perspective

HLA-HDR pharmacogenomic associations are very rarely studied in the GME populations. Gene candidate studies or GWAS, in GME populations, may discover new associations or confirm associations reported with a low level of evidence. The advent NGS and the scalability of the various bioinformatic tools that have been developed to achieve HLA genotyping provide an interesting opportunity to reduce knowledge gap in the characterization of HLA-HDR associations in the GME-populations. Further studies genotyping HLA and further studies identifying pharmacogenomic markers are expected in the near future from the GME, particularly in the populations where genomic projects are ongoing. The high ethnic variability of HLA genes should particularly motivate studying HLA-HDRs pharmacogenomic associations in different populations of the GME.

Executive summary

- Adverse drug reactions could be life threatening, particularly type B hypersensitivity drug reactions (HDRs).
- HDRs are associated with specific alleles of the HLAs.
- Most of the discovered associations were based on studies including populations from Asia and Western countries.
- The high ethnic variability of HLA genes should particularly motivate the study of HLA-HDR pharmacogenomic associations in different populations of the world.
- Genome wide association and case–control studies would confirm known associations and allow for the discovery of new pharmacogenomic markers in the Greater Middle East populations where HLA-drug hypersensitivity has been rarely studied.
- Only the study and the confirmation of any HLA-HDR associations in a specific population allow the cost–effectiveness evaluation of screening the allele, in this population, before drug use.

Author contributions

H Chaker and G Tay conceived the preparation of this review. Subsequently, H Chaker produced the first draft and worked with N Afify to prepare the manuscript with contributions from G Tay, H Alnaqbi, Z Alhalwachi and H Al Safar. All coauthors read, reviewed and edited versions of the manuscript.

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