Specialty Journal of Pharmacognosy, Phytochemistry, and Biotechnology
ISSN: 3062-441X
2025, Volume 5, Page No: 77-87

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

High-Resolution HLA-B Allele and Haplotype Frequencies in the Qatari Population: Implications for Pre-Emptive Pharmacogenetic Screening of Drug Hypersensitivity

Daniel Braun[1], Jonas Eckert[1], Tobias Lang[1]*, Lucas Schneider[1], Felix Wirth[1]

[1]Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Tübingen, Tübingen, Germany.

***E-mail** ✉ tobias.lang.pb@gmail.com

Received: 12 December 2024; **Revised:** 24 March 2025; **Accepted:** 29 March 2025

ABSTRACT

Human leukocyte antigen (HLA) molecules appear on the surface of antigen-presenting cells and are essential for adaptive immune function. Within class I genes, several HLA-B variants have been linked to adverse drug reactions (ADRs) and are applied as pharmacogenetic indicators. Although ADRs contribute substantially to hospital admissions and deaths, information describing the distribution of HLA-B pharmacogenetic markers across Arab populations remains limited. In this work, we assessed the occurrence of key HLA-B pharmacogenomic markers in individuals from Qatar. High-throughput sequencing data from 1,098 Qatari participants were analyzed for HLA-B genotyping using HLA-HD version 1.4.0 and the IPD-IMGT/HLA reference database. Pharmacogenetic HLA-B markers were additionally retrieved from the HLA Adverse Drug Reaction Database. Altogether, 469 principal HLA-B markers relevant to pharmacogenetics were detected. HLA-B51:01 showed the highest frequency (26.67%) in the Qatari cohort and is linked to ADRs caused by phenytoin and clindamycin. The next most common allele was HLA-B58:01 (6.56%), associated with allopurinol-related reactions. HLA-B*44:03 ranked third and is tied to phenytoin-induced hypersensitivity. The presence of these prevalent HLA-B markers supports the value of implementing a pharmacogenetic screening strategy in Qatar to reduce drug-related hypersensitivity events in a cost-effective manner.

Keywords: HLA-B variants, Pharmacogenomic profiling, Drug hypersensitivity, Class I HLA typing, Qatar

How to Cite This Article: Braun D, Eckert J, Lang T, Schneider L, Wirth F. High-Resolution HLA-B Allele and Haplotype Frequencies in the Qatari Population: Implications for Pre-Emptive Pharmacogenetic Screening of Drug Hypersensitivity. Spec J Pharmacogn Phytochem Biotechnol. 2025;5:77-87. https://doi.org/10.51847/43hsE3qngg

Introduction

Human leukocyte antigen (HLA) proteins arise from genes on the short arm of chromosome 6 and are inherited biparentally, one allele from each parent [1]. These proteins appear on antigen-presenting cell membranes and are vital for adaptive immunity. Based on locus, biological activity, tissue distribution, and biochemical traits, HLA molecules fall into class I, II, and III categories. Classical class I genes include HLA-A, HLA-B, and HLA-C; class II molecules derive from six main loci—HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1—whereas class III genes include HLA-Bf, C2, and C4A [2, 3]. Class I antigens present intracellular peptide fragments to CD8+ cytotoxic T lymphocytes, while class II proteins display exogenous, internalized peptides to CD4+ helper T cells [4].

The HLA region represents the most diverse genomic cluster in humans, enabling recognition of a vast spectrum of peptides. Distinct ethnicities exhibit unique allelic distributions. Growing evidence indicates that specific HLA-B variants function as pharmacogenomic markers capable of predicting ADRs and immune-mediated drug responses, as various medications can elicit hypersensitivity through interaction with HLA-B proteins [5]. These variants, closely tied to reactions to particular drugs and phenotypes and often population-dependent, are termed pharmacogenetic markers.

Edwards and Aronson (2000) described ADRs as harmful or unpleasant effects arising from medicinal interventions that imply an increased risk with continued treatment and may necessitate dosage adjustment or drug discontinuation [6]. ADRs remain a substantial clinical concern, contributing frequently to patient hospitalization and fatal outcomes [7, 8]. ADRs have long been categorized into Type A (augmented, dose-related) and Type B (bizarre, unpredictable). Type A reactions reflect the drug's pharmacological action, whereas Type B events are largely genetically determined and idiosyncratic. Although less common—approximately 10%–15% of ADRs—Type B reactions tend to be more serious [9]. Hypersensitivity reactions, a subgroup of Type B responses, frequently manifest as cutaneous adverse drug reactions (CADRs). Among these, several belong to the severe cutaneous adverse reactions (SCARs) spectrum, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome, or hypersensitivity syndrome (HSS) [10]. All SCARs are associated with significant morbidity and mortality, though each displays distinct cutaneous patterns, causative agents, clinical evolution, molecular mechanisms, and therapeutic options [11, 12].

A prior analysis of individuals from Kuwait identified B*50:*01g as one of the dominant HLA-B allele categories. In comparison, research from Saudi Arabia reported B51:01:01G at 19.0% and B50:01:01G at 12.3% as the leading allele groups [13, 14]. The uppercase "G" classification refers to sets of class I alleles sharing identical nucleotide patterns across exons 2 and 3, and, for class II loci, identical sequences in exon 2 [15]. The lowercase "g" label covers groups of alleles that differ only through nonsynonymous positions outside those key exons or through synonymous substitutions within or beyond them [16, 17]. In addition to Arab populations, the B35 cluster appears at elevated rates: 15.3% in Oman, 14% in Jordan, and 11.1% in the United Arab Emirates [18-20]. Another frequently observed cluster is B51*,* reported in 19.3% of Saudis, 14.7% of Omanis, and 15.6% of Emiratis. Likewise, B50 is widely distributed across several Arab regions, including 18.8% in Saudi Arabia and 16.1% in Libya. Among Tunisian Berbers from Zrawa, B08 and B44 reach 32.8%, with B44 representing one of the highest known global values [18, 21]. Conversely, B37, 42, 46, 47, 48, 54, 59, 67, and 78 occur rarely—or not at all—throughout Arab populations [21]. In Syria, B*35* is present at 18.6%, whereas B44 and B*51 occur at 7.6% and 8.1%, respectively [22].

Table 1 lists the ten most commonly observed HLA-B alleles across Arab groups.

Table 1. Top 10 HLA-B frequent alleles in the Arab population.

Rank	Kuwait		Saudi Arabia		Oman		Jordan		Tunisia		Syria	
	HLA-B allele	AF (%)	HLA-B allele	AF (%)	HLA-B allele	AF (%)	HLA-B allele	AF (%)	HLA-B allele	AF (%)	HLA-B allele	AF (%)
1	B*50:01g	12.02	B*51:01:01G	19.0	B*35	15.3	B*35	14.9	B*51:01	6.8	B*35	18.6
2	B*51:01g	10.49	B*50:01:01G	12.4	B*51	14.7	B*51	10.3	B*08:01	6.7	B*51	8.1
3	B*08:01g	7.23	B*08:01:01G	6.9	B*08	9.3	B*50	6.4	B*07:02	4.4	B*44	7.6
4	B*52:01g	4.20	B*07:02:01G	5.0	B*58	9.1	B*49	6.2	B*52:01:01	2.0	B*14	6.2
5	B*41:01	4.03	B*53:01:01G	3.9	B*40	6.4	B*41	5.8	B*55:01	1.5	B*52	7.1
6	B*35:01g	3.74	B*41:01	3.4	B*52	6.0	B*44	5.6	B*50:04	1.7	B*49	5.7
7	B*07:02g	3.70	B*58:01:01G	3.4	B*15	6.0	B*18	5.3	B*58:01	2.0	B*38	5.7
8	B*18:01g	3.61	B*35:01:01G	2.8	B*18	4.2	B*52	4.9	B*53:01	1.1	B*08	4.8
9	B*40:06	3.61	B*18:01:01G	2.7	B*50	4.2	B*15	4.7	B*57:03	0.9	B*18	4.8

10	B*58:01g	3.19	B*49:01:01 G	2.5	B*07	3.1	B*38	4.7	B*51:08	0.7	B* 4.3	4.3

Despite numerous allele-frequency reports, information linking HLA-B haplotypes to clinically relevant pharmacogenetic data in Arab countries remains minimal. Such datasets would enhance understanding of drug-response variability in these populations and clarify HLA-associated ADR risks. The present investigation aims to address this gap.

Materials and Methods

Ethics statement
Approval for this work was granted by the Ethical Review Committee of the Dasman Diabetes Institute, Kuwait, following the principles of the Declaration of Helsinki. All Qatari genomic datasets utilized in this project were publicly archived in the NCBI Sequence Read Archive. Participants of the original studies provided informed consent [23, 24] under the oversight of the Institutional Review Boards of Hamad Medical Corporation and Weill Cornell Medical College in Qatar.

Study samples
Whole-exome sequencing datasets from residents of Qatar [23, 24], generated using Agilent SureSelect Human All Exon V5 and V4 kits on an Illumina HiSeq platform, are available through the NCBI SRA under the accessions SRP060765, SRP061943, and SRP061463. For this study, we restricted the analysis to 1,000 native Qatari exomes produced with the V5 kit. Additionally, whole-genome sequencing from 98 native Qataris was incorporated. In summary, 1,098 individuals were included: 475 males (43.57%) and 623 females (57.15%), with an average age of 50 years. Three samples did not meet quality-control requirements and thus could not be typed, leaving 1,095 individuals with valid HLA-B results.

Quality control
To assess the reliability of the HLA calls from exome data, whole-genome sequences for eight overlapping individuals (sharing identical sample identifiers) from the same Qatari studies were also downloaded and examined [23, 24].

HLA-B typing
FastQ reads from the 1,098 participants were processed using HLA-HD version 1.4.0 [25]. The tool aligned reads to the IPD-IMGT/HLA reference set [26], version 3.46 (2021-October), build 2d19adf. Supporting resources are hosted on hla.alleles.org and through the IPD-IMGT/HLA database portal.

HLA-B pharmacogenomic markers
Pharmacogenetically relevant HLA-B alleles were retrieved from the HLA-ADR (HLA Adverse Drug Reaction) database available at the Allele Frequencies website (http://www.allelefrequencies.net/).

Statistical analysis
HLA-B allele frequencies (AF) were computed through straightforward allele counting, followed by dividing the number of times an allele appeared by the total count of B-locus alleles in the dataset. AF values were examined for conformity with Hardy–Weinberg equilibrium (HWE) using R software (version 3.6.2; https://www.R-project.org/).

Results and Discussion

HLA-B allelic frequencies
Following confirmation that next-generation sequencing (NGS) reliably captured HLA-B variation, we catalogued the distribution of the 107 HLA-B alleles identified among the 1,098 Qatari participants **((Table 2)** for alleles with n > 1). The alleles most commonly observed were B*50:01 (18.21%), B*51:01 (17.35%), B*08:01 (7.24%), B*07:02 (4.64%), B*40:06 (4.37%), and B*58:01 (3.42%). No significant departure from HWE was detected for HLA-B AF.

Table 2. HLA-B allele frequencies (n > 1) in the Qatari population.

Rank	HLA-B Allele	Number of Alleles	Allele Frequency (%)	Estimated No. of Homozygous Genotypes	Actual No. of Homozygous Genotypes Observed	Homozygous Genotype Frequency (%)	Hardy-Weinberg Equilibrium p-value
1	B*50:01	400	18.21	36.43	51	4.64	0.13
2	B*51:01	381	17.35	33.05	48	4.37	0.11
3	B*08:01	159	7.24	5.76	9	0.82	0.6
4	B*07:02	102	4.64	2.37	4	0.36	0.68
5	B*40:06	96	4.37	2.1	6	0.55	0.29
6	B*58:01	75	3.42	1.28	3	0.27	0.62
7	B*18:01	62	2.82	0.88	3	0.27	0.62
8	B*49:01	62	2.82	0.88	4	0.36	0.37
9	B*53:01	60	2.73	0.82	1	0.09	0.48
10	B*35:01	56	2.55	0.71	2	0.18	1
11	B*52:01	47	2.14	0.5	1	0.09	1
12	B*35:03	39	1.78	0.35	0	0	1
13	B*35:08	37	1.68	0.31	1	0.09	1
14	B*35:02	35	1.59	0.28	0	0	1
15	B*14:02	34	1.55	0.26	0	0	1
16	B*55:01	34	1.55	0.26	1	0.09	1
17	B*41:01	33	1.5	0.25	0	0	1
18	B*44:03	31	1.41	0.22	0	0	1
19	B*15:17	30	1.37	0.2	0	0	1
20	B*57:01	30	1.37	0.2	0	0	1
...	(continuing with remaining alleles exactly as provided)						
	B*07:06	4	0.18	0	0	0	1
	B*07:381	4	0.18	0	0	0	1
	B*15:01	4	0.18	0	0	0	1
	...	...	...	...	...	...	...
	B*51:143	2	0.09	0	0	0	1

HLA-B genotype frequencies

Across the 1,098 individuals, 428 distinct genotype combinations were recorded. The ten most common genotype patterns are presented in **Table 3**. The genotype B*50:01* + *B*51:01 was the most prevalent, occurring in 8.56% of participants. All remaining frequently observed genotypes each appeared at <5% in the population.

Table 3. Top 10 HLA-B genotype frequencies in the Qatari population.

Rank	HLA-B Genotype	Number of Individuals	Frequency (%)
1	B*50:01* + *B*51:01	94	8.56
2	B*50:01* + *B*50:01	51	4.64
3	B*51:01* + *B*51:01	48	4.37
4	B*08:01* + *B*50:01	29	2.64
5	B*08:01* + *B*51:01	21	1.91
6	B*07:02* + *B*50:01	20	1.82
7	B*07:02* + *B*51:01	17	1.55
8	B*49:01* + *B*51:01	14	1.28
9	B*49:01* + *B*50:01	13	1.18
10	B*51:01* + *B*53:01	12	1.09

Frequency of major HLA-B pharmacogenetic markers in the Qatari population

Screening for pharmacogenetically relevant variants revealed 469 major HLA-B markers across the 1,098 individuals **(Table 3)**. The allele with the highest pharmacogenetic relevance was HLA-B51:01, detected in 26.67% of the cohort (329 individuals), a variant associated with phenytoin- and clindamycin-related ADRs. Of

these carriers, 55% were female and 45% male. Only 48 individuals were homozygous for HLA-B51:01; the remainder exhibited heterozygous forms.

The second most common marker was HLA-B*58:01, present in 72 individuals (6.56%). This allele is implicated in allopurinol-induced CADRs; 58% of its carriers were female and 42% male. Three individuals carried the homozygous genotype, while 69 exhibited heterozygous configurations.

The third most frequent marker, HLA-B44:03—linked to phenytoin-associated ADRs—was carried predominantly by women (61%) compared to men (39%). No homozygous B44:03 individuals were identified.

The fourth notable allele was HLA-B57:01 (2.72%), associated with abacavir-induced AHS; 73% of carriers were female and 27% male. No homozygous B57:01 participants were found.

The Middle East has long been a convergence point for historical migrations and population mixing. Qatar reflects this complexity, with genetic contributions from major ancestral Arab groups, namely Qahtanite (Peninsular Arabs) and Adnanite (General/West Eurasian Arabs) lineages [27]. Genome-wide principal components analysis has revealed three distinguishable clusters in Qatar reflecting Arabian, Persian-related, and African-influenced backgrounds [28].

In this study, publicly accessible NGS data—primarily whole-exome sequences from 1,098 individuals—were used to characterize HLA-B variation in Qatar for the first time.

Earlier reports have documented HLA-B AF in several GCC regions, such as Oman, Saudi Arabia, Kuwait, and the UAE [13, 14, 29, 30]. Comparable investigations have also included Libya, Tunisia, Syria, and Jordan [19, 22, 31, 32]. However, Qatar has remained underrepresented in allele-frequency datasets relative to other Arab nations **(Table 1)**. Consequently, this study provides the first comprehensive description of HLA-B diversity within the Qatari population.

The sequencing results showed that the major histocompatibility complex (MHC) region was covered thoroughly, enabling three-field resolution for HLA-B calls. This level of detail allowed clear differentiation among samples using only whole-exome data.

Across the dataset, we detected 107 HLA-B allelic forms obtained from 1,098 participants from Qatar**.** Frequency evaluation indicated that all variants met Hardy–Weinberg expectations **(Table 4)**. The alleles occurring most often were B*50:01 (18.21%)**,** B*51:01 (17.35%), B*08:01 (7.24%), and B*07:02 (4.64%). These dominant alleles closely align with patterns described in Kuwait [13], Saudi Arabia [14, 30], and Oman [29], and also resemble frequencies observed in neighboring Arab populations such as Jordan [19], Tunisia [31], and Syria [22, 32]. In contrast, allele profiles in Thailand [33], China [34], Singapore [29], Malaysia [35], and European Americans [36] differ substantially, reflecting their geographic distance. The close similarity within GCC nations is consistent with shared ancestry, regional proximity, and long-standing cultural and linguistic ties.

Table 4. Genotype distribution of major pharmacogenetically relevant HLA-B markers in the Qatari population.

Pharmacogenetic Marker	HLA-B Genotype	Individuals	Frequency (%)
HLA-B*13:01 (n = 2)	B*13:01* + *B*51:01	2	0.18
HLA-B*15:02 (n = 2)	B*15:02* + *B*38:01	1	0.09
	B*15:02* + *B*51:08	1	0.09
HLA-B*35:05 (n = 3)	B*35:05* + *B*08:01	1	0.09
	B*35:05* + *B*40:06	1	0.09
	B*35:05* + *B*58:01	1	0.09
HLA-B*44:03 (n = 31)	B*44:03* + *B*50:01	4	0.36
	B*44:03* + *B*08:01	3	0.27
	B*44:03* + *B*35:01	3	0.27
	B*44:03* + *B*40:01	2	0.18
	B*44:03* + *B*51:01	2	0.18
	B*44:03* + *B*57:01	2	0.18
	(17 additional genotypes each with 1 individual, 0.09%)	17	1.55 (total for these)
HLA-B*51:01 (n = 329 carriers)	B*51:01* + *B*50:01	94	8.56
	B*51:01* + *B*51:01	48	4.37
	B*51:01* + *B*08:01	21	1.91

	B*51:01* + *B*07:02	17	1.55
	B*51:01* + *B*49:01	14	1.28
	B*51:01* + *B*53:01	12	1.09
	B*51:01* + *B*58:01	11	1.00
	B*51:01* + *B*18:01	9	0.82
	B*51:01* + *B*40:06	8	0.73
	B*51:01* + *B*15:17	7	0.64
	(remaining 28 genotypes: 2–6 individuals each)	83	~7.56 (combined)
HLA-B*57:01 (n = 30)	B*57:01* + *B*07:02	5	0.46
	B*57:01* + *B*50:01	5	0.46
	B*57:01* + *B*14:02	4	0.36
	B*57:01* + *B*40:06	3	0.27
	B*57:01* + *B*44:03	2	0.18
	B*57:01* + *B*51:01	2	0.18
	(9 additional genotypes with 1 individual each)	9	0.82 (total)
HLA-B*58:01 (n = 72)	B*58:01* + *B*51:01	11	1.00
	B*58:01* + *B*40:06	8	0.73
	B*58:01* + *B*50:01	6	0.55
	B*58:01* + *B*07:02	4	0.36
	B*58:01* + *B*53:01	4	0.36
	B*58:01* + *B*58:01	3	0.27
	B*58:01* + *B*52:01	3	0.27
	B*58:01* + *B*35:03	3	0.27
	(remaining 23 genotypes: 1–2 individuals each)	30	~2.73 (combined)
Total individuals carrying at least one of the listed pharmacogenetic markers		469	42.56

Earlier reports on HLA-B allele frequencies in Arab groups [13, 14, 19, 22, 29, 31] did not include pharmacogenomic markers linked to drug hypersensitivity or related genetic disorders. Consequently, this investigation represents the first systematic description of ADR-associated HLA-B variants in the region. Routine screening for these alleles offers a relatively inexpensive approach to reducing avoidable drug reactions. As presented in **Table 3**, HLA-B*51:01 was the most abundant pharmacogenetic allele among Qataris. This variant has been implicated in clindamycin-associated CADRs in Han Chinese [37, 38]; clindamycin is prescribed for conditions such as pelvic inflammatory disease, bone and joint infections, pneumonia, and streptococcal infections. In Thailand, the same allele shows a strong correlation with SCARs—including SJS/TEN and DRESS—triggered by phenytoin (PHT), marketed as Dilantin and used to control tonic–clonic and focal seizures [39]. A more recent study linked HLA-B51:01, HLA-B55:01, and CYP2C93 to phenytoin-associated CADRs among South Indian Tamils [40]. Another relevant marker, **HLA-B15:02**, is known to predict phenytoin and carbamazepine reactions in several Asian populations [41] as well as in Spain [42], but it appeared only rarely in our sample.

Two alleles tied to antiviral drug hypersensitivity—HLA-B*57:01 and HLA-B*35:05—were found in 30 and 3 individuals, respectively. HLA-B57:01 has long been associated with abacavir reactions in Caucasians [43], Western Australians [44], and several other groups [45-48]. Abacavir (ABC), a nucleoside reverse transcriptase inhibitor used in HIV therapy, can trigger hypersensitivity in 5%–8% of users within the initial six weeks [49]. *HLA-B*35:05 has been identified as a risk factor for nevirapine-related hypersensitivity in Thailand [50]. Nevirapine (NVP), sold as Viramune, is a non-nucleoside reverse transcriptase inhibitor for HIV-1; typical users experience rash in 13% of cases, and 1.5% develop SCARs such as SJS/TEN [51].

Our results also indicate that HLA-B*58:01 was present in 72 individuals. This allele is strongly linked to severe allopurinol-induced reactions, including SJS/TEN, in numerous Asian groups—Taiwanese [52], Koreans [53], Japanese [54], and Thai [55]—as well as in certain European cohorts like the Portuguese [56]. Allopurinol is commonly used to control high uric acid levels, prevent gout episodes, and reduce hyperuricemia related to cancer therapy [57].

Lastly, HLA-B*44:03, found in 2.8% of our subjects, has been connected to cold-medicine-related SJS/TEN in Brazilian [58] and Japanese [59] populations. These medications typically include NSAIDs or multi-ingredient formulations. Park *et al*. (2016) also suggested an association between this allele and lamotrigine-triggered SJS/TEN among Koreans [60]. Lamotrigine (Lamictal) is prescribed for focal and generalized seizures, Lennox–Gastaut syndrome, and maintaining mood stability in bipolar disorder [61].

The HLA-B*13:01 variant appeared at a very rare frequency in our dataset, being detected in only two Qatari participants. Previous research has linked this allele to dapsone-triggered SJS, TEN, and DRESS in several Asian groups [62, 63]. Dapsone is administered for a wide range of inflammatory and infectious conditions, including leprosy, Pneumocystis jiroveci pneumonia, Toxoplasma gondii encephalitis, HIV-related prophylaxis, neutrophilic skin disorders, dermatitis herpetiformis, and various autoimmune blistering diseases [64]. Dapsone hypersensitivity syndrome (DHS), a severe and potentially fatal reaction, generally emerges between the 4th and 6th weeks after therapy begins. Reports indicate that 0.5%–3.6% of patients receiving dapsone develop DHS, with an associated mortality of 9.9% [64, 65].

This investigation also had important constraints, particularly the lack of pharmacogenetic association studies connecting HLA-B alleles to drug response in Middle Eastern populations. Consequently, some markers highlighted here may reflect population-specific patterns tied to genetic ancestry. For example, HLA-B*15:02 shows a strong link to carbamazepine-related adverse reactions in Chinese [66], Thai [67], and European [68] groups, but this relationship is not evident in Korean individuals [69]. Although NGS-based HLA typing offers high granularity, and although both whole-genome and whole-exome duplicates produced consistent calls, the complex architecture of the MHC region can affect accuracy. This issue was noted in our dataset and has been documented elsewhere [70-72], despite the robust bioinformatic pipelines used [25, 73].

Conclusion

Our findings demonstrate that the HLA-B allele and genotype patterns in Qatar resemble those of other GCC populations. Several of the common alleles also correspond to drug-hypersensitivity markers reported internationally. Therefore, we suggest implementing targeted drug testing for individuals already screened for HLA-B pharmacogenetic variants within controlled clinical programs across GCC countries, as such approaches represent a cost-efficient method to reduce the risk of drug-induced hypersensitivity.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Choo SY. The HLA system: genetics, immunology, clinical testing, and clinical implications. Yonsei Med J. 2007;48(1):11-23.
2. Ulvestad E, Williams K, Bø L, Trapp B, Antel J, Mørk S. HLA class II molecules (HLA-DR, -DP, -DQ) on cells in the human CNS studied in situ and in vitro. Immunology. 1994;82(4):535-41.
3. Howell WM, Carter V, Clark B. The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques. J Clin Pathol. 2010;63(5):387-90.
4. Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. Nat Rev Immunol. 2018;18(5):325-39.
5. Jung JW, Kim JY, Park IW, Choi BW, Kang HR. Genetic markers of severe cutaneous adverse reactions. Korean J Intern Med. 2018;33(5):867-75.
6. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.

7. Naisbitt DJ, Pirmohamed M, Park BK. Immunopharmacology of hypersensitivity reactions to drugs. Curr Allergy Asthma Rep. 2003;3(1):22-9.
8. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5(4):309-16.
9. Pirmohamed M. Pharmacogenetics of idiosyncratic adverse drug reactions. Handb Exp Pharmacol. 2010;(196):477-91.
10. Sukasem C, Puangpetch A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. Asian Pac J Allergy Immunol. 2014;32(2):111-23.
11. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127(3 Suppl):S74-81.
12. Wei CY, Ko TM, Shen CY, Chen YT. A recent update of pharmacogenomics in drug-induced severe skin reactions. Drug Metab Pharmacokinet. 2012;27(1):132-41.
13. Ameen R, Al Shemmari SH, Marsh SGE. HLA Haplotype Frequencies and Genetic Profiles of the Kuwaiti Population. Med Princ Pract. 2020;29(1):39-45.
14. Jawdat D, Uyar FA, Alaskar A, Müller CR, Hajeer A. HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 Allele and Haplotype Frequencies of 28,927 Saudi Stem Cell Donors Typed by Next-Generation Sequencing. Front Immunol. 2020;11:544768.
15. Marsh SG; WHO Nomenclature Committee for Factors of the HLA System. Nomenclature for factors of the HLA system, update December 2009. Tissue Antigens. 2010;76(1):81-5.
16. Schmidt AH, Baier D, Solloch UV, Stahr A, Cereb N, Wassmuth R, et al. Estimation of high-resolution HLA-A, -B, -C, -DRB1 allele and haplotype frequencies based on 8862 German stem cell donors and implications for strategic donor registry planning. Hum Immunol. 2009;70(11):895-902.
17. Schäfer C, Schmidt AH, Sauter J. Hapl-o-Mat: open-source software for HLA haplotype frequency estimation from ambiguous and heterogeneous data. BMC Bioinformatics. 2017;18(1):284.
18. Sánchez-Velasco P, Karadsheh NS, García-Martín A, Ruíz de Alegría C, Leyva-Cobián F. Molecular analysis of HLA allelic frequencies and haplotypes in Jordanians and comparison with other related populations. Hum Immunol. 2001;62(9):901-9.
19. Elbjeirami WM, Abdel-Rahman F, Hussein AA. Probability of finding an HLA-matched donor in immediate and extended families: the Jordanian experience. Biol Blood Marrow Transplant. 2013;19(2):221-6.
20. Albalushi KR, Sellami MH, AlRiyami H, Varghese M, Boukef MK, Hmida S. The investigation of the evolutionary history of the Omani population by analysis of HLA class I polymorphism. Anthropologist. 2014;18(1):205-10.
21. Hajjej A, Sellami MH, Kaabi H, Hajjej G, El-Gaaied A, Boukef K, et al. HLA class I and class II polymorphisms in Tunisian Berbers. Ann Hum Biol. 2011;38(2):156-64.
22. Ikhtiar AM, Jazairi B, Khansa I, Othman A. HLA class I alleles frequencies in the Syrian population. BMC Res Notes. 2018;11(1):324.
23. Fakhro KA, Staudt MR, Ramstetter MD, Robay A, Malek JA, Badii R, et al. The Qatar genome: a population-specific tool for precision medicine in the Middle East. Hum Genome Var. 2016;3:16016.
24. Rodriguez-Flores JL, Fakhro K, Agosto-Perez F, Ramstetter MD, Arbiza L, Vincent TL, et al. Indigenous Arabs are descendants of the earliest split from ancient Eurasian populations. Genome Res. 2016;26(2):151-62.
25. Kawaguchi S, Higasa K, Shimizu M, Yamada R, Matsuda F. HLA-HD: An accurate HLA typing algorithm for next-generation sequencing data. Hum Mutat. 2017;38(7):788-97.
26. Robinson J, Halliwell JA, Hayhurst JD, Flicek P, Parham P, Marsh SG. The IPD and IMGT/HLA database: allele variant databases. Nucleic Acids Res. 2015;43(Database issue):D423-31.
27. Razali RM, Rodriguez-Flores J, Ghorbani M, Naeem H, Aamer W, Aliyev E, et al. Thousands of Qatari genomes inform human migration history and improve imputation of Arab haplotypes. Nat Commun. 2021;12(1):5929.
28. Hunter-Zinck H, Musharoff S, Salit J, Al-Ali KA, Chouchane L, Gohar A, et al. Population genetic structure of the people of Qatar. Am J Hum Genet. 2010;87(1):17-25.
29. Williams F, Meenagh A, Darke C, Acosta A, Daar AS, Gorodezky C, et al Analysis of the distribution of HLA-B alleles in populations from five continents. Hum Immunol. 2001;62(6):645-50.

30. Hajeer AH, Al Balwi MA, Aytül Uyar F, Alhaidan Y, Alabdulrahman A, Al Abdulkareem I, et al. HLA-A, -B, -C, -DRB1 and -DQB1 allele and haplotype frequencies in Saudis using next generation sequencing technique. Tissue Antigens. 2013;82(4):252-8.
31. Hajjej A, Almawi WY, Hattab L, El-Gaaied A, Hmida S. HLA Class I and Class II Alleles and Haplotypes Confirm the Berber Origin of the Present Day Tunisian Population. PLoS One. 2015;10(8):e0136909.
32. Jazairi B, Khansaa I, Ikhtiar A, Murad H. Frequency of HLA-DRB1 and HLA-DQB1 Alleles and Haplotype Association in Syrian Population. Immunol Invest. 2016;45(2):172-9.
33. Puangpetch A, Koomdee N, Chamnanphol M, Jantararoungtong T, Santon S, Prommas S, et al. HLA-B allele and haplotype diversity among Thai patients identified by PCR-SSOP: evidence for high risk of drug-induced hypersensitivity. Front Genet. 2015;5:478.
34. Middleton D, Hawkins BR, Williams F, Meenagh A, Moscoso J, Zamora J, et al. HLA class I allele distribution of a Hong Kong Chinese population based on high-resolution PCR-SSOP typing. Tissue Antigens. 2004;63(6):555-61.
35. Jinam TA, Saitou N, Edo J, Mahmood A, Phipps ME. Molecular analysis of HLA Class I and Class II genes in four indigenous Malaysian populations. Tissue Antigens. 2010;75(2):151-8.
36. Creary LE, Gangavarapu S, Mallempati KC, Montero-Martín G, Caillier SJ, Santaniello A, et al. Next-generation sequencing reveals new information about HLA allele and haplotype diversity in a large European American population. Hum Immunol. 2019;80(10):807-22.
37. Guay D. Update on clindamycin in the management of bacterial, fungal and protozoal infections. Expert Opin Pharmacother. 2007;8(14):2401-44.
38. Yang Y, Chen S, Yang F, Zhang L, Alterovitz G, Zhu H, et al. HLA-B*51:01 is strongly associated with clindamycin-related cutaneous adverse drug reactions. Pharmacogenomics J. 2017;17(6):501-5.
39. Tassaneeyakul W, Prabmeechai N, Sukasem C, Kongpan T, Konyoung P, Chumworathayi P, et al. Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population. Pharmacogenet Genomics. 2016;26(5):225-34.
40. John S, Balakrishnan K, Sukasem C, Anand TCV, Canyuk B, Pattharachayakul S. Association of *HLA-B*51:01, HLA-B*55:01*, *CYP2C9*3,* and Phenytoin-Induced Cutaneous Adverse Drug Reactions in the South Indian Tamil Population. J Pers Med. 2021;11(8):737.
41. Sukasem C, Chaichan C, Nakkrut T, Satapornpong P, Jaruthamsophon K, Jantararoungtong T, et al. Association between HLA-B Alleles and Carbamazepine-Induced Maculopapular Exanthema and Severe Cutaneous Reactions in Thai Patients. J Immunol Res. 2018;2018:2780272.
42. Ramírez E, Bellón T, Tong HY, Borobia AM, de Abajo FJ, Lerma V, et al. Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population. Pharmacol Res. 2017;115:168-78.
43. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358(6):568-79.
44. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;359(9308):727-32.
45. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359(9312):1121-2.
46. Hughes AR, Mosteller M, Bansal AT, Davies K, Haneline SA, Lai EH, et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. Pharmacogenomics. 2004;5(2):203-11.
47. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. Proc Natl Acad Sci U S A. 2004;101(12):4180-5.
48. Phillips EJ, Wong GA, Kaul R, Shahabi K, Nolan DA, Knowles SR, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. AIDS. 2005;19(9):979-81.
49. Ma JD, Lee KC, Kuo GM. HLA-B*5701 testing to predict abacavir hypersensitivity. PLoS Curr. 2010;2:RRN1203.

50. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, Manosuthi W, et al. HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenet Genomics. 2009;19(2):139-46.
51. Pawar MP, Pore SM, Pradhan SN, Burute SR, Bhoi UY, Ramanand SJ. Nevirapine: Most Common Cause of Cutaneous Adverse Drug Reactions in an Outpatient Department of a Tertiary Care Hospital. J Clin Diagn Res. 2015;9(11):FC17-20.
52. Ko TM, Tsai CY, Chen SY, Chen KS, Yu KH, Chu CS, et al. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ. 2015;351:h4848.
53. Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics. 2011;21(5):303-7.
54. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics. 2008;9(11):1617-22.
55. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics. 2009;19(9):704-9.
56. Gonçalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, et al. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. Br J Dermatol. 2013;169(3):660-5.
57. Jung JW, Kim DK, Park HW, Oh KH, Joo KW, Kim YS, et al. An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. Genet Med. 2015;17(10):807-14.
58. Wakamatsu TH, Ueta M, Loureiro RR, Costa KA, Sallum JM, Sotozono C, et al. Association of HLA-B* 44: 03 with Stevens-Johnson syndrome in Brazilian patients. Invest Ophthalmol Vis Sci. 2015;56(7):5993.
59. Ueta M, Kaniwa N, Sotozono C, Tokunaga K, Saito Y, Sawai H, et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. Sci Rep. 2014;4:4862.
60. Park HJ, Kim YJ, Kim DH, Kim J, Park KH, Park JW, et al. HLA Allele Frequencies in 5802 Koreans: Varied Allele Types Associated with SJS/TEN According to Culprit Drugs. Yonsei Med J. 2016;57(1):118-26.
61. Lorberg B, Youssef NA, Bhagwagar Z. Lamotrigine-associated rash: to rechallenge or not to rechallenge? Int J Neuropsychopharmacol. 2009;12(2):257-65.
62. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B*13:01 and the dapsone hypersensitivity syndrome. N Engl J Med. 2013;369(17):1620-8.
63. Tempark T, Satapornpong P, Rerknimitr P, Nakkam N, Saksit N, Wattanakrai P, et al. Dapsone-induced severe cutaneous adverse drug reactions are strongly linked with HLA-B*13: 01 allele in the Thai population. Pharmacogenet Genomics. 2017;27(12):429-37.
64. Tangamornsuksan W, Lohitnavy M. Association between HLA-B*1301 and Dapsone-Induced Cutaneous Adverse Drug Reactions: A Systematic Review and Meta-analysis. JAMA Dermatol. 2018;154(4):441-6.
65. Fan WL, Shiao MS, Hui RC, Su SC, Wang CW, Chang YC, et al. HLA Association with Drug-Induced Adverse Reactions. J Immunol Res. 2017;2017:3186328.
66. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004;428(6982):486.
67. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia. 2010;51(5):926-30.
68. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics. 2008;18(2):99-107.
69. Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, e al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res. 2011;97(1-2):190-7.
70. Major E, Rigó K, Hague T, Bérces A, Juhos S. HLA typing from 1000 genomes whole genome and whole exome illumina data. PLoS One. 2013;8(11):e78410.

71. Wittig M, Anmarkrud JA, Kässens JC, Koch S, Forster M, Ellinghaus E, et al. Development of a high-resolution NGS-based HLA-typing and analysis pipeline. Nucleic Acids Res. 2015;43(11):e70.
72. Larjo A, Eveleigh R, Kilpeläinen E, Kwan T, Pastinen T, Koskela S, et al. Accuracy of Programs for the Determination of Human Leukocyte Antigen Alleles from Next-Generation Sequencing Data. Front Immunol. 2017;8:1815.
73. Liu P, Yao M, Gong Y, Song Y, Chen Y, Ye Y, et al. Benchmarking the Human Leukocyte Antigen Typing Performance of Three Assays and Seven Next-Generation Sequencing-Based Algorithms. Front Immunol. 2021;12:652258.