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Original Article

Association of Human Leukocyte Antigen Alleles with Carbamazepine- or Lamotrigine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in an Iranian Population: A Case-control Study

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What's Known

- HLA alleles play a key role in drug-induced severe cutaneous adverse reactions (SCARs). An association between HLA-B*1502 and carbamazepine (CBZ)/lamotrigine (LTG)-induced Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN) was reported.
- There are conflicting results on the association between HLA alleles and anti-epileptic drug-induced SCARs in the Iranian population.

What's New

- No association was found between the HLA-B*1502 allele and CBZ/LTG-induced SJS/TEN in an Iranian population.
- The main strength of this study is that it compares various HLA allele data from drug-induced SJS/TEN patients with both drug-tolerant patients and a normal population.

Abstract

Background: Genetic diversity in human leukocyte antigen (HLA) alleles across populations is a significant risk factor for drug-induced severe cutaneous adverse reactions (SCARs), e.g., carbamazepine (CBZ)- and lamotrigine (LTG)-induced Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The present study aimed to investigate the frequency of different HLA alleles in Iranian patients with CBZ- and LTG-induced SJS/TEN.

Methods: A case-control study was conducted from 2011 to 2018 at various hospitals affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). A total of 31 patients receiving anticonvulsant drugs (CZB or LTG) were recruited and divided into two groups. The drug-induced group (n=14) included hospitalized patients due to CBZ- or LTG-induced SJS/TEN. The drug-tolerant group (n=17) included individuals receiving CBZ or LTG for at least three months with no adverse effects. In addition, 46 healthy individuals (control group) were recruited. The frequency of HLA-A, -B, and -DRB1 alleles in patients with CZB- or LTG-induced SJS/TEN was investigated. HLA typing was performed using the allele-specific polymerase chain reaction method. The Chi square test and Fisher's exact test were used to determine a potential association between SJS/TEN and HLA alleles. $P<0.05$ was considered statistically significant.

Results: CBZ- or LTG-induced SJS/TEN was not significantly associated with HLA alleles. However, HLA-DRB1*01 showed a significantly higher frequency in patients with CBZ-induced SJS/TEN than the CBZ-tolerant patients (30% *vs.* 9%, P=0.07).

Conclusion: Overall, no significant association was found between CBZ- or LTG-induced SJS/TEN and HLA alleles. Further large-scale studies are required to substantiate our findings.

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Keywords ● Stevens-Johnson syndrome ● Anticonvulsants ● Histocompatibility testing

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis

(TEN) are types of severe cutaneous adverse reactions (SCARs) involving the skin, oro-genital, and ocular mucosa. SJS and TEN, with a mortality rate of 3% and 27%, respectively, are characterized by erythematous or dusky red patches, atypical targetoid lesions, bullae, erosions, and skin detachment after using certain medications.[1] Anticonvulsant drugs are the most common cause of drug-induced adverse reactions, accounting for 10% to 30% of all reported cases. Carbamazepine (CBZ) is an effective drug in the treatment of epilepsy, neuralgia, and bipolar disorders. Lamotrigine (LTG), phenytoin, phenobarbital, nonsteroidal anti-inflammatory drugs, and allopurinol are considered the main drugs with possible adverse reactions.[2, 3]

While the pathogenesis of SJS/TEN needs further clarification, genetic factors including drug metabolism pathways and immune system properties are considered the main etiologic factors to cause SJS/TEN.[4] The first report on the association between SJS/TEN and immune-related factors was published in 1987, introducing specific human leukocyte antigen (HLA) molecules associated with oxicam- and sulfonamide-induced TEN in a European population.[5] Subsequently, several HLA alleles and genetic polymorphisms of the cytochrome P450 2C subfamily were found associated with drug-induced SJS/TEN.[6, 7] From an immunological perspective, drug-induced SJS/TEN can be categorized as a delayed-type hypersensitivity (DTH) reaction. The presentation of drug-peptide complexes by the major histocompatibility complex (MHC) and subsequent recognition of these complexes by T cells leads to a cascade of immune activation of cytotoxic T cells as well as natural killer cells and cytokine production.[4, 8]

HLA proteins are highly polymorphic molecules and important factors in antigen-specific immune activation. Different HLA alleles bind to different peptides, resulting in the activation of different T cell clones.[9] Due to the genetic diversity in HLA frequencies across populations and ethnicities and the role of HLA molecules in trigging drug-induced SJS/TEN, the association of HLA alleles with drug-induced SJS/TEN was investigated in several populations.[10] In the case of CBZ, a strong association between the HLA-B*1502 allele and CBZ-induced SJS was reported in the Han Chinese population.[11] However, studies conducted among Caucasians did not show such a correlation, indicating the important role of ethnicity in genetic predisposition.[12] The incidence of CBZ-induced epidermal toxic necrolysis and SJS in several Asian countries was reported to be ten times higher than that in the European countries and the United States.[13] On the other hand, HLA alleles such as HLA-B*4001, HLA-B*4601, and HLA-B*5801 were shown to have a protective role against CBZ-induced SJS/TEN. In terms of LTG-induced SJS/TEN, HLA-B*1502 and HLA-A*2402 were reported to have the strongest association in different populations.[14]

Given the importance of HLA molecules in SJS/TEN and the strong effect of ethnicity on HLA polymorphism, this study aimed to investigate the frequency of HLA-A, -B, and -DRB1 alleles with CBZ- and LTG-induced SJS/TEN in Iranian patients of Persian ethnicity.

Patients and Methods

A case-control study was conducted from 2011 to 2018 at various hospitals affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). A total of 31 patients receiving anticonvulsant drugs were recruited and divided into two groups, namely the drug-induced group (n=14) and the drug-tolerant group (n=17). The drug-induced group included patients hospitalized due to CBZ-induced SJS/TEN (n=10) or LTG-induced SJS/TEN (n=4). The drug-tolerant group included individuals receiving CBZ (n=11) or LTG (n=6) for at least three months without adverse effects. Individuals in the drug-tolerant group were selected among those treated at the Epilepsy Clinic affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). In addition, based on HLA genotyping data, 46 healthy individuals (control group) were recruited among those who attended Fars Blood Transfusion Organization (Shiraz, Iran). All participants in the treated groups were sex and drug matched and were from the same geographical region and ethnicity.

SJS/TEN was diagnosed by a dermatologist, primarily based on clinical features and pathology reports (if indicated). The main clinical criterion for SJS and TEN was the involvement of <10% and >30% of the body surface area, respectively.[1] Patients taking other medications in addition to CBZ or LTG were excluded from the study. Peripheral blood samples (3 mL) of all participants were collected in ethylenediaminetetraacetic acid (EDTA) tubes and stored for further use.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1394.S355). Written informed consent was obtained from the participants, and voluntary participation was emphasized.

HLA Typing

Genomic DNA was extracted from blood samples using a commercial DNA extraction kit (Genet Bio, Nonsan, South Korea) according to the manufacturer's instructions. HLA-A, -B, and -DRB1 were genotyped using the allele-specific polymerase chain reaction (PCR-SSP) method. To this end, low-resolution commercial kits with pre-designed primers were used (Texas BioGene, Texas, USA). The PCR procedures were performed according to the manufacturer's recommendations. PCR products were electrophoresed on 2% agarose gel and visualized under ultraviolet light. Genotypes were determined by an expert in HLA typing based on visualized patterns according to the manufacturer's instructions.

Statistical Analysis

Data were analyzed using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). The Chi square test and Fisher's exact test were used to determine a potential association between SJS/TEN and HLA alleles. $P<0.05$ was considered statistically significant.

Results

The mean age of the patients in the drug-induced and drug-tolerant groups was 23.6±16.2 and 24.4±17.9 years, respectively. The participants in these groups were of Persian ethnic origin and consisted of 16 women and 15 men. All patients suffered from epilepsy except for one patient who was diagnosed with post-herpetic neuralgia.

The frequency of HLA alleles was initially analyzed in CBZ-induced SJS/TEN and CBZ-tolerant patients. There was no statistically significant association between CBZ-induced SJS/TEN and HLA alleles. However, HLA-DRB1*01 showed a significantly higher frequency in patients with CBZ-induced SJS/TEN compared to CBZ-tolerant patients (30% *vs.* 9%, P=0.07). Similarly, no significant association was found between LTG-induced SJS/TEN and other HLA alleles.

Due to the low number of patients receiving LTG, we only analyzed the frequencies of HLA alleles in CBZ-induced SJS/TEN patients. The frequency of HLA-B, -DRB1, and -A in both drug-induced and drug-tolerant groups are presented in tables 1, 2, and 3, respectively. Briefly, no significant association was found between CBZ- or LTG-induced SJS/TEN and any of the investigated HLA alleles. Indeed, some of the alleles such as HLA-A*11, HLA-A*32, HLA-B*08, HLA-B*14, HLA-B*15, HLA-B*40, HLA-DRB1*01, and HLA-DRB1*16 were more frequent in the drug-induced group than

Table 1: The frequency of HLA-B alleles in the drug-induced and drug-tolerant groups

HLA-B alleles	CBZ- or LTG-induced SJS/TEN (n, %) (N=28)	CBZ- or LTG-tolerant (n, %) (N=34)	P value	Control group (n, %) (N=92)
07	0 (0)	1 (2.9)	>0.999	3 (3.26)
08	2 (7.1)	0 (0)	0.38	4 (4.34)
13	0 (0)	0 (0)	-	3 (3.26)
14	2 (7.1)	0 (0)	0.38	2 (2.17)
15	2 (7.1)	0 (0)	0.38	3 (3.26)
18	0 (0)	2 (5.9)	0.56	8 (8.69)
27	0 (0)	0 (0)	-	1 (1.08)
35	3 (10.7)	10 (29.4)	0.14	21 (22.82)
38	2 (7.1)	2 (5.9)	>0.999	3 (3.26)
39	0 (0)	0 (0)	-	2 (2.17)
40	3 (10.7)	0 (0)	0.17	2 (2.17)
41	0 (0)	4 (11.8)	0.22	5 (5.43)
42	0 (0)	0 (0)	-	1 (1.08)
44	2 (7.1)	1 (2.9)	0.86	1 (1.08)
45	0 (0)	0 (0)	-	2 (2.17)
49	0 (0)	0 (0)	-	2 (2.17)
50	1 (3.6)	2 (5.9)	>0.999	1 (1.08)
51	7 (25)	5 (14.7)	0.48	14 (15.21)
52	0 (0)	5 (14.7)	0.15	9 (9.78)
53	1 (3.6)	0 (0)	0.92	0 (0)
55	1 (3.6)	0 (0)	0.92	0 (0)
57	0 (0)	0 (0)	-	1 (1.08)
58	0 (0)	1 (2.9)	0.38	4 (4.34)
73	2 (7.1)	1 (2.9)	0.86	0 (0)

HLA: Human leukocyte antigens; CBZ: Carbamazepine; LTG: Lamotrigine; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis

Table 2: The frequency of HLA-DRB1 alleles in the drug-induced and drug-tolerant groups

HLA-DRB1 alleles	CBZ- or LTG-induced SJS/TEN (n, %) (N=28)	CBZ- or LTG-tolerant (n, %) (N=34)	P value	Control group (n, %) (N=92)
01	6 (21)	3 (8.8)	0.29	6 (6.52)
03	2 (7.1)	4 (11.7)	0.85	12 (13.04)
04	2 (7.1)	4 (11.7)	0.85	6 (6.52)
07	3 (10.7)	2 (5.8)	0.82	6 (6.52)
08	1 (3.5)	0 (0)	0.92	1 (1.08)
09	0 (0)	0 (0)	-	0 (0)
10	0 (0)	1 (2.9)	0.38	0 (0)
11	5 (17.8)	7 (20.5)	>0.999	25 (27.17)
12	0 (0)	1 (2.9)	0.38	0(0)
13	1 (3.5)	1 (2.9)	>0.999	5 (5.43)
14	2 (7.1)	2 (5.8)	>0.999	5 (5.43)
15	2 (7.1)	8 (23.5)	0.16	16 (17.39
16	4 (14.2)	1 (2.9)	0.24	9 (9.78)

HLA: Human leukocyte antigens; CBZ: Carbamazepine; LTG: Lamotrigine; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis

Table 3: The frequency of HLA-A alleles in the drug-induced and drug-tolerant groups

HLA-A alleles	CBZ- or LTG-induced SJS/TEN (n, %) (N=28)	CBZ- or LTG-tolerant (n, %) (N=34)	P value	Control group (n, %) (N=92)
01	3 (10.7)	4 (11.7)	>0.999	12 (13.04)
02	4 (14.2)	7(20.5)	0.75	14 (15.21)
03	3 (10.7)	4(11.7)	>0.999	9 (9.78)
11	4 (14.2)	2 (5.8)	0.49	7 (7.60)
16	1 (3.5)	0 (0)	0.92	0 (0)
23	0 (0)	0 (0)	-	1 (1.08)
24	3 (10.7)	6 (17.6)	0.68	1 (1.08)
26	2 (7.1)	3 (8.8)	>0.999	4 (4.34)
29	0 (0)	0 (0)	-	5 (5.43)
30	0 (0)	0 (0)	-	5 (5.43)
31	0 (0)	0 (0)	-	2 (2.17)
32	4 (14.2)	2 (5.8)	0.49	6 (6.52)
33	1 (3.5)	1 (2.9)	-	4 (4.34)
66	1 (3.5)	1 (2.9)	-	1 (1.08)
68	2 (7.1)	4 (11.7)	0.58	5 (5.43)

HLA: Human leukocyte antigens; CBZ: Carbamazepine; LTG: Lamotrigine; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis

the drug-tolerant group (A*11: 14.2% *vs.* 5.8, A*32: 14.2% *vs.* 5.8%, B*08: 7.1% *vs.* 0%, B*14: 7.1% *vs.* 0%, B*15: 7.1% *vs.* 0%, B*40: 10.7% *vs.* 0%, DRB1*01: 21% *vs.* 8.8%, and DRB1*16: 14.2% *vs.* 2.9%). However, none of these were statistically significant.

Discussion

The results of the present study showed no significant association between HLA alleles and the risk of developing SJS/TEN following CBZ or LTG use. However, there was a marginal association between HLA-DRB1*01 and CBZ use (P=0.07). Moreover, the frequency of some of the HLA alleles was higher in the drug-induced group than the drug-tolerant group.

In the case of CBZ, several studies investigated different HLA alleles in different populations. The most known HLA allele associated with CBZ-induced SJS/TEN is HLA-B*1502. This allele was reported to be strongly associated with CBZ-induced SJS/TEN in Chinese, Korean, Japanese, and Indian populations.[15-18] Based on the reported data on CBZ use, the United States Food and Drug Administration recommended genotyping all Asians for the HLA-B*1502 allele.[19] A previous study reported that HLA-B*1502 has the potential for strong binding affinity to CBZ and that CBZ could bind to this HLA allele without any intracellular processes.[20] However, some other studies reported no association between CBZ-induced SJS/TEN and HLA-B*1502 in a Caucasian population.[12] A recent study on an Iranian population have shown that, compared

to phenytoin-induced SJS/TEN, the risk of LTG-induced SJS/TEN was significantly higher in patients with HLA-B*1502 (8 *vs.* 28 patients, respectively).[21] Another study reported no association between HLA-B*1502 and severe anticonvulsant drug-induced skin reactions in Iranian children.[22] The results of these studies in Iran are in line with our results showing no significant association with HLA-B*15. This could be due to the low frequency of HLA-B*15 and HLA-B*1502 in the Iranian normal population as reported in our study (3.3%) and another study (0%).[23]

Considerable heterogeneities in the association between HLA alleles and CBZ-induced SJS/TEN are reported in the literature. A systematic review investigating CBZ-related hypersensitivity showed that HLA-B*1502 and HLA-B*1511 are the main alleles associated with a severe form of CBZ-induced hypersensitivity in an Asian population. However, in the same population, HLA-A*2402 was introduced as a protective allele. Besides, HLA-A*3101 was reported as the most frequent risk factor in all populations.[24] Another study conducted in Iran reported the association of HLA-A*0201, HLA-A*2402, and HLA-B*5101 with an increased risk of developing SJS. However, this study only compared the frequency of HLA alleles in SJS pediatric patients and healthy individuals but did not include drug-tolerant patients.[23]

In our study, the only allele that was marginally associated with CBZ was HLA-DRB1*01 (P=0.07). Although most studies investigated HLA class I in association with CBZ-induced SJS/TEN, few examined HLA class II. In one of these studies, carried out in Italy, DRB1*1502 and DRB1*1302 alleles were reported at significantly increased frequency in CBZ-induced SJS/TEN patients.[25] A study on a Japanese population, however, showed no association between SJS and any of the HLA-DRB1 alleles.[15]

In the case of LTG-induced SJS/TEN, despite the very small sample size, we found no association with any of the investigated HLA alleles (data not shown). We even found no association when both LTG- and CBZ-induced SJS/TEN were considered as a group. In a meta-analysis study of Asian populations, HLA-B*1502 was suggested as a risk factor for LTG-induced SJS/TEN in a Chinese population, and HLA-A*2402 was associated with the susceptibility to SJS/TEN. Reportedly, HLA-A*3303 is a protective allele against LTG-induced hypersensitivity in Chinese and Korean populations.[10]

Our results showed that CBZ- or LTG-induced SJS/TEN in an ethnic Persian population was not significantly associated with HLA alleles. However, given the different ethnicities in Iran, large-scale multicenter studies are recommended to obtain a comprehensive set of results. In addition, more accurate results can be achieved using high-resolution HLA genotyping.

Conclusion

Overall, no significant association was found between carbamazepine- or lamotrigine-induced SJS/TEN and HLA alleles. Further large-scale studies are required to substantiate our findings.

Authors' Contribution

L.D, F.R, B.Gh.F, A.A.A.P, S.N, F.T and M.H.B: conception and design; acquisition, analysis, and interpretation of data for the work, drafting and revising. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

References

1 Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333:1600-7. doi: 10.1056/NEJM199512143332404. PubMed PMID: 7477195.

2 Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272-85. doi: 10.1056/NEJM199411103311906. PubMed PMID: 7794310.

3 Lim KS, Kwan P, Tan CT. Association of HLA-B* 1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review. Neurol Asia. 2008;13:15-21.

4 Schneider JA, Cohen PR. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. Adv Ther. 2017;34:1235-44. doi: 10.1007/s12325-017-0530-y. PubMed PMID: 28439852; PubMed Central PMCID: PMCPMC5487863.

5 Roujeau JC, Huynh TN, Bracq C, Guillaume

JC, Revuz J, Touraine R. Genetic susceptibility to toxic epidermal necrolysis. Arch Dermatol. 1987;123:1171-3. PubMed PMID: 3477129.
6 Saito Y, Kodama S, Sugiyama E, Nakamura R. [Predictive genomic markers for severe adverse drug reactions]. Yakugaku Zasshi. 2015;135:589-95. doi: 10.1248/yakushi.14-00249-3. PubMed PMID: 25832839.
7 Cheng CY, Su SC, Chen CH, Chen WL, Deng ST, Chung WH. HLA associations and clinical implications in T-cell mediated drug hypersensitivity reactions: an updated review. J Immunol Res. 2014;2014:565320. doi: 10.1155/2014/565320. PubMed PMID: 24901010; PubMed Central PMCID: PMCPMC4034438.
8 Su SC, Chung WH. Cytotoxic proteins and therapeutic targets in severe cutaneous adverse reactions. Toxins (Basel). 2014;6:194-210. doi: 10.3390/toxins6010194. PubMed PMID: 24394640; PubMed Central PMCID: PMCPMC3920257.
9 Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. Nat Rev Immunol. 2018;18:325-39. doi: 10.1038/nri.2017.143. PubMed PMID: 29292391.
10 Deng Y, Li S, Zhang L, Jin H, Zou X. Association between HLA alleles and lamotrigine-induced cutaneous adverse drug reactions in Asian populations: A meta-analysis. Seizure. 2018;60:163-71. doi: 10.1016/j.seizure.2018.06.024. PubMed PMID: 30015149.
11 Zhang Y, Wang J, Zhao LM, Peng W, Shen GQ, Xue L, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. Eur J Clin Pharmacol. 2011;67:885-7. doi: 10.1007/s00228-011-1009-4. PubMed PMID: 21424386.
12 Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. Pharmacogenomics. 2006;7:813-8. doi: 10.2217/14622416.7.6.813. PubMed PMID: 16981842.
13 Wang YH, Chen CB, Tassaneeyakul W, Saito Y, Aihara M, Choon SE, et al. The Medication Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Asians: The Major Drug Causality and Comparison With the US FDA Label. Clin Pharmacol Ther. 2019;105:112-20. doi: 10.1002/cpt.1071. PubMed PMID: 29569740.
14 Wang Q, Sun S, Xie M, Zhao K, Li X, Zhao Z. Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: A meta-analysis. Epilepsy Res. 2017;135:19-28. doi: 10.1016/j.eplepsyres.2017.05.015. PubMed PMID: 28618376.
15 Ueta M, Tokunaga K, Sotozono C, Inatomi T, Yabe T, Matsushita M, et al. HLA class I and II gene polymorphisms in Stevens-Johnson syndrome with ocular complications in Japanese. Mol Vis. 2008;14:550-5. PubMed PMID: 18385790; PubMed Central PMCID: PMCPMC2274925.
16 Wang Q, Zhou JQ, Zhou LM, Chen ZY, Fang ZY, Chen SD, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. Seizure. 2011;20:446-8. doi: 10.1016/j.seizure.2011.02.003. PubMed PMID: 21397523.
17 Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res. 2011;97:190-7. doi: 10.1016/j.eplepsyres.2011.08.010. PubMed PMID: 21917426.
18 Aggarwal R, Sharma M, Modi M, Garg VK, Salaria M. HLA-B * 1502 is associated with carbamazepine induced Stevens-Johnson syndrome in North Indian population. Hum Immunol. 2014;75:1120-2. doi: 10.1016/j.humimm.2014.09.022. PubMed PMID: 25305458.
19 Ferrell PB, Jr., McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9:1543-6. doi: 10.2217/14622416.9.10.1543. PubMed PMID: 18855540; PubMed Central PMCID: PMCPMC2586963.
20 Wei CY, Chung WH, Huang HW, Chen YT, Hung SI. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. J Allergy Clin Immunol. 2012;129:1562-9. doi: 10.1016/j.jaci.2011.12.990. PubMed PMID: 22322005.
21 Sabourirad S, Mortezaee R, Mojarad M, Eslahi A, Shahrokhi Y, Kiafar B, et al. Investigating the association of Lamotrigine and Phenytoin-induced Stevens-Johnson syndrome/Toxic Epidermal Necrolysis with HLA-B*1502 in Iranian population. Exp Dermatol. 2021;30:284-7. doi: 10.1111/exd.14240. PubMed PMID: 33217035.

22 Tonekaboni SH, Jafari N, Mansouri M, Jabbehdari S, Eftekhari R, Chavoshzadeh Z, et al. HLA-B*1502 in Iranian Children with Anticonvulsant Drugs-Induced Skin Reactions. Iran J Child Neurol. 2017;11:26-30. PubMed PMID: 28698724; PubMed Central PMCID: PMCPMC5493826.

23 Esmaeilzadeh H, Farjadian S, Alyasin S, Nemati H, Nabavizadeh H, Esmaeilzadeh E. Epidemiology of Severe Cutaneous Adverse Drug Reaction and Its HLA Association among Pediatrics. Iran J Pharm Res. 2019;18:506-22. PubMed PMID: 31089385; PubMed Central PMCID: PMCPMC6487414.

24 Grover S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet Genomics. 2014;24:94-112. doi: 10.1097/FPC.0000000000000021. PubMed PMID: 24336023.

25 Cristallo AF, Schroeder J, Citterio A, Santori G, Ferrioli GM, Rossi U, et al. A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. Int J Immunogenet. 2011;38:303-9. doi: 10.1111/j.1744-313X.2011.01011.x. PubMed PMID: 21545408.