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Original Article

Exploring the link between carbamazepine- and lamotrigine-induced skin reactions and the HLA-A31:01 and HLA-B*1502 genetic markers

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Summary

Introduction: Anticonvulsant drugs are valuable treatments for seizures and epilepsy. Carbamazepine (CBZ) and lamotrigine (LTG) are antiepileptic and mood-stabilizing drugs used to treat these diseases. The study aimed to investigate the relationship between the side effects of CBZ and LTG and the HLA-B*1502 and HLA-A31:01 alleles in Iranian patients with a seizure disorder.

Methods: This cross-sectional study was conducted on patients diagnosed with convulsions who visited Imam Reza and Razi Educational-Therapeutic Center, affiliated with Tabriz University of Medical Sciences, between March 2018 and March 2022. The blood samples of patients were analyzed by polymerase chain reaction for the presence or absence of HLA-B*1502 and HLA-A31:01 alleles.

Findings: In the HLA genetic analysis, the frequency of HLA-A31:01 was found to be 3.1%, and all three carriers of the HLA-A31:01 allele were in the first group; however, the difference between the studied groups was not statistically significant ($P=0.07$). The prevalence of the HLA-B 1502 gene in low resolution was 5.2%, which included 2 (4.2%) patients in the first group and 3 (6.1%) patients in the second group ($P=0.66$). None of these patients carried the HLA-B 1502 genotype in the high-resolution analysis. In the subgroup analysis of CBZ recipients, the prevalence of HLA-A31:01 was found to be 4.5%, and all three HLA-A31:01 patients were in the first group; however, the difference between the examined groups was not statistically significant ($P>0.05$). In the LTG subgroup analysis, HLA-B15:02 did not indicate a significant difference between the two groups ($P>0.05$).

Conclusion: In the present study, which involved 97 patients, no correlation was found between the genetic markers HLA-B*1502 and HLA-A31:01 and skin reactions triggered by antiepileptic drugs.

Keywords: Carbamazepine, Lamotrigine, Anticonvulsant drugs, Genetics

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Introduction

Anticonvulsant drugs are a valuable treatment to control seizures and epilepsy in patients. Carbamazepine (CBZ) and lamotrigine (LTG) are antiepileptic and mood-stabilizing drugs that are used to treat these diseases and cases such as trigeminal neuralgia and chronic pain.[1-4] However, adverse drug reactions can lead to patient disability and mortality, while significantly burdening the healthcare system. Each year, over two million individuals experience such side effects, resulting in approximately 106 000 deaths.[5,6]

Common side effects of CBZ include nausea, vomiting, confusion, drowsiness, dry mouth, tongue swelling, imbalance and disorientation.[7] Common side effects of LTG include tremors, dizziness, weakness, red-blue vision, diplopia, imbalance, dry mouth, abdominal pain, nausea, and back pain.[8] Mucocutaneous side effects related to CBZ and LTG use can cause a range of symptoms from urticaria to severe drug side effects of hypersensitivity syndrome (HSS), associated with serious cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis syndrome (TENS) or overlapping of these two syndromes.[9,10] SJS presents as erythematous, purpuric macules, or flat, atypical target lesions affecting less than 10% of the body surface. When 10%-30% of the surface is involved, it is classified as an SJS-TENS overlap. In cases where more than 30% of the body surface is affected, the condition is categorized as TENS.[11] Involvement of the gastrointestinal and tracheobronchial systems significantly raises the mortality rate of this syndrome. Additionally, immunological and skin impairments greatly increase the risk of infections and complications like sepsis.[12] The prevalence of SJS is estimated at 1-6 cases per 1 million people per year,

and the majority of TENS is estimated at 0.4-1.2.[13] The mortality rate in SJS is estimated to be 1%-5% and in TENS, up to 30%.[14]

Genetic factors, particularly genetic diversity in human leukocyte antigen (HLA) alleles, play a crucial role in the susceptibility to aforementioned reactions across populations. Due to the existence of numerous studies in different regions and races to determine the relationship between HLA-B*1502 and HLA-A31:01 with the complications caused by CBZ and LTG consumption, this study aimed to investigate the frequency of HLA-B*1502 and HLA-A31:01 alleles in Iranian patients with a seizure disorder.

Methods

Subjects

This comparative prospective cross-sectional study was conducted on patients with seizure disorders who visited one of Imam Reza or Razi educational-therapeutic centers affiliated with Tabriz University of Medical Sciences between March 2018 and March 2022. The target population consisted of patients with seizure disorders, divided into two groups. The first group included patients who experienced skin-mucosal complications due to CBZ or LTG consumption. In contrast, the second group consisted of people with seizure disorders who did not have complications related to CBZ or LTG usage. After explaining the purpose of the study and the procedures involved, informed consent was obtained from the patients.

Inclusion criteria consisted of patients with seizure disorders being treated with CBZ or LTG, specifically those for whom CBZ or LTG was identified as the cause of drug side effects (without the use of any medications with similar side effects two months before experiencing these side effects), Additionally, patients needed to be either admitted to the ward or referred to the clinic were included. The exclusion criteria included patients with bullous autoimmune diseases, skin rashes or blisters associated with infectious diseases, vasculitis, severe drug-induced skin reactions following bone marrow transplantation, concurrent use of medications with similar side effects, and those unwilling to participate in the study.

The patients were included in the study provided they met the criteria for participation, ensuring confidentiality of their information, the voluntary nature of the study, and approval of the informed consent form. The clinical records of patients were reviewed to document the types of complications, along with personal details such as age, sex, and the dosage and duration of the medications used in the study.

Genetic analysis

Blood samples (5 cc) were collected from all subjects in EDTA tubes to prevent coagulation. Genomic DNA was extracted from whole blood samples using a standard phenol-chloroform method. The PCR method was employed to type HLA-B*1502 and HLA-A31:01 alleles using Olerup SSP HLA Typing Kits (Germany). The resulting data were subsequently evaluated.

Statistical analysis

The data were statistically analyzed using IBM SPSS software (version 24; SPSS, Chicago, IL). Qualitative data were reported as descriptive statistics (frequency and percentage), and quantitative data were reported as mean ± SD if normal. Also, ratio comparison tests (chi-square or Fisher's exact test) were used to compare the ratio of drug side effects in the two groups. In all statistical tests, the significance level of $P<0.05$ was considered, and the 95% confidence limit was observed.

Results

This study was conducted on 97 patients divided into group one (48 patients) and group two (49 patients). The general characteristics of the studied patients are reported in Table 1. There was no significant difference between the patients of the two groups in terms of age and gender ($P>0.05$). Among all participants, 67 (69.1%) patients received CBZ, and 30 (30.9%) patients received LTG. There was no statistically significant difference between the studied groups regarding the type of drug usage ($P=0.34$).

Regarding the type of seizures, focal seizures were reported in 60 (61.9%) patients, generalized seizures in 29 (29.9%) patients, and mixed seizures in 8 (8.2%) patients. There was no significant statistical difference in seizure type between the case and control groups ($P=0.74$). In the first group, patients were assessed for the severity of allergic reactions: 43 patients (89.6%) experienced mild reactions, while 5 patients (10.4%) had SJS.

In HLA genetic analysis, the frequency of the HLA-A31:01 allele was found to be 3.1%, with all carriers belonging to the first group; however, the difference between the studied groups was not statistically significant ($P>0.05$). The prevalence of the HLA-B 1502 allele in low resolution was 5.2%, which included 2 (4.2%) patients in the first group and 3 (6.1%) patients in the second group ($P=0.66$). None of these patients exhibited the HLA-B1502 genotype in the high-resolution analysis. Table 2 presents the overall characteristics of CBZ recipients in the study, highlighting comparisons between the examined groups. In this subgroup analysis, there were no significant differences between the two groups regarding age, gender, and seizure type ($P>0.05$). In the HLA genetic analysis, the prevalence of HLA-A31:01 was 4.5%, with all three patients carrying this allele in the first group; however, the difference between the examined groups was not statistically significant ($P=0.05$). All

Table1. General characteristics of study participants and comparison between the studied groups

Variable	Total sample size (n=97)	Group 1 (n=48)	Group 2 (n=49)	*P* value
Age	35.57±9.76	36.29±9.38	34.86±9.74	0.475
Female	55(56.7%)	31 (64.6%)	24(49.0%)	0.121
Male	42 (43.3%)	17(35.4%)	25 (51.0%)	
HLA-A31:01 in Low-resolution	3 (3.1%)	3(%6.3)	0	0.074
HLA-B15:02 in Low-resolution	5(%5.2)	2(%4.2)	3(%6.1)	0.662
Drug				
CBZ	67(%69.1)	31(%64.6)	36(%73.5)	0.342
LTG	30(%30.9)	17(%35.4)	13(%26.5)	
Seizure type				
Focal	60(%61.9)	29(%60.4)	31(%63.3)	0.742
Generalized	29(%29.9)	14(%29.2)	15(%30.6)	
Mixed	8(%8.2)	5(%10.4)	3(%6.1)	
The severity of the allergic reaction				
Mild	-	43(%89.6)	-	-
SJS	-	5(%10.4)	-	-

Group 1: patients who experienced skin-mucosal complications due to CBZ or LTG consumption.
Group 2: consisted of people with seizure disorders who did not have complications related to CBZ or LTG usage.
CBZ: Carbamazepine; LTG: Lamotrigine; SJS, Stevens-Johnson syndrome.
Significance of variables ($P<0.05$).

HLA-A31:01 patients who showed an allergic reaction had received CBZ. The frequency of the HLA-B 1502 gene was 6.0% in the low-resolution study, including 2 (6.5%) patients in the first group and 2 (5.6%) patients in the second group ($P=0.872$). None of these patients carried the HLA-B 1502 genotype in the high-resolution analysis. Furthermore, as shown in Table 2, the significant result regarding the dose of CBZ is found in the p-value of 0.041, which indicates a statistically significant difference between the two groups regarding CBZ dosage.

In other words, group 1 received lower doses (200–400 mg) more frequently and patients in group 2 received higher doses (800 mg and above) more often. The statistically significant value suggests that CBZ dosage may be associated with the presence or absence of complications.

Table 3 reports the study's general characteristics of LTG recipients and compares studied groups. In this subgroup analysis, there was no significant difference between the studied groups in terms of age, gender, and seizure type ($P>0.05$). Considering that all HLA-A31:01 patients who showed an allergic reaction had received CBZ, it was impossible to investigate the role of HLA-A31:01 in the occurrence of complications caused by LTG in this study. HLA-B15:02 allele was present in only 1 (7.7%) patient in group 2 in the Low-resolution analysis, which did not indicate a significant difference between the groups ($P>0.05$).

Table 2. The overall characteristics of CBZ recipients in the study, highlight comparisons between the examined groups

Variable	Total sample size (n=67)	Group 1 (n=31)	Group 2 (n=36)	*P* value
Age	34.73±9.40	35.16±9.00	34.36±9.85	0.731
Female	31% (46.3)	16% (51.6)	15(48.4%)	0.411
Male	36% (53.7)	15(41.7%)	21(58.3%)	
HLA-A31:01 in Low-resolution	3(4.5%)	3(9.7%)	0	0.050
HLA-B15:02 in Low-resolution	4(6.0%)	2(6.5%)	2(5.6%)	0.872
HLA- B15:02 in High-resolution	0	0	0	-
Seizure type				
Focal	48(71.6%)	23(74.2%)	25(69.4%)	0.593
Generalized	16(23.9%)	6(19.4%)	10(27.8%)	
Mixed	3(4.5%)	2(6.5%)	1(2.8%)	
The dose of the CBZ (mg)				
200	7(10.4%)	4(12.9%)	3(8.3%)	*0.041
400	31(46.3%)	19(61.3%)	12(33.3%)	
600	8(11.9%)	5(16.3%)	3(8.3%)	
800	13(19.4%)	2(6.5%)	11(30.6%)	
1000	20% (3)	0	5(26%)	
1200	7(55%)	3(12%)	11(41%)	
1600	1(15%)	0	2(18%)	

Group 1: patients who experienced skin-mucosal complications due to CBZ or LTG consumption.
Group 2: consisted of people with seizure disorders who did not have complications related to CBZ or LTG usage.
CBZ: Carbamazepine
Significance of variables ($P<0.05$).

Discussion

The results of the present study indicated that HLA-A31:01 and HLA-B 1502 did not show a significant relationship with the incidence of hypersensitivity caused by CBZ and LTG consumption.

Delayed hypersensitivity reactions that occur more than 6 hours after drug administration are mediated by T-cells and are associated with specific HLA alleles, opening avenues for clinical prediction and prevention. However, the low positive predictive value and the extensive number of tests needed to rule out a case have hindered the large-scale and cost-effective implementation of screening.[15] HLA genes form the most polymorphic gene clusters in the human genome, where the most remarkable allelic diversity is concentrated in the peptide binding sites of HLA molecules. HLA-B*1502 and HLA-A*3101 have been identified as genetic markers predicting CBZ hypersensitivity.[16] The results of a meta-analysis study on sixteen articles concluded a strong association between HLA-B*1502 and CBZ-induced SJS and TENS in Malaysian, Thai, and Han-Chinese, populations.[17] Some HLA alleles are also significantly associated with SCARs caused by drugs such as CBZ and LTG.[18] Despite the established link in many Asian populations, the

Table 3. The overall characteristics of LTG recipients in the study, highlight comparisons between the examined groups

Variable	All participants (n = 30)	Group 1 (n = 17)	Group 2 (n = 13)	*P* value
Age	37.43 ± 10.44	38.35 ± 11.19	36.23 ± 9.68	0.591
Female	24(%80.0)	15(%88.2)	9(%69.2)	0.197
Male	6(%20.0)	2(%11.8)	4(%30.8)	
HLA-A31:01 in Low-resolution	0	0	0	-
HLA-B15:02 in Low-resolution	1(%3.3)	0	1(%7.7)	0.245
HLA- B15:02 in High-resolution	0	0	0	-
Seizure type				
Focal	12(%40.0)	6(%35.3)	6(%46.2)	0.834
Generalized	13(%43.3)	8(%47.1)	5(%38.5)	
Mixed	5(%16.7)	3(%17.6)	2(%15.4)	
The dose of LTG (mg)				
100	5(%16.7)	4(%23.5)	1(%7.7)	0.423
150	14(%46.7)	9(%52.9)	5(%38.5)	
200	5(%16.7)	2(%11.8)	3(%23.1)	
300	5(%16.7)	2(%11.8)	3(%23.1)	
350	1(%3.3)	0	1(%7.7)	

Group 1: patients who experienced skin-mucosal complications due to CBZ or LTG consumption.
Group 2: consisted of people with seizure disorders who did not have complications related to CBZ
or LTG usage.
LTG: Lamotrigine
Significance of variables ($P<0.05$).

results of this study and some other studies have reported conflicting results. Our finding was in line with the study of Tenkabani et al,[19] who did not observe any association between HLA-B*1502 and severe skin reactions caused by taking anticonvulsants in Iranian children. This highlights the importance of considering genetic backgrounds when assessing risk factors for drug-induced skin reactions.

Unlike HLA-B*15:02, which is restricted mainly to Southeast Asia, HLA-A*31:01 exists in many different populations worldwide. The frequency of the HLA-A*31:01 allele in European populations is between 2.1 and 3.6%.[20,21] In a study conducted on the recommendation of the US Food and Drug Administration, the prevalence of the HLA-B*1502 allele was reported to be high in the Chinese and East Asian populations. Still, this fact was not actual for the Caucasian population.[22] In this study, the prevalence of HLA-A31:01 was 3.1%, and the majority of the HLA-B 1502 gene was 0.0% in the High-resolution study, similar to the European population in the study population.

Studies confirm the association between HLA-A*31:01 carrier and increased susceptibility to CBZ-induced allergic reactions. At the same time, the association with HSS seems clear from all studies; whether HLA-A*31:01 is also associated with maculopapular exanthema (MPE)[23] and SJS-TEN is more controversial. The discrepancy between studies is likely due to small sample sizes, misclassification/misdiagnosis of cases, and difficulty determining causality, especially in milder cases.[23] HLA-A31:01 has been linked to CBZ-induced hypersensitivity reactions in various populations, including European and Japanese patients. However, pharmacogenetic screening is not currently mandatory before initiating CBZ therapy. Only the Canadian Pharmacogenomics Network for Safety Drug recommends testing for HLA-A31:01 in patients of all ancestries to minimize the risk of hypersensitivity reactions. Research has highlighted the cost-effectiveness of genetic screening before prescribing certain medications, and one study specifically examined the economic viability of pharmacogenetic screening for HLA-A*31:01 before CBZ treatment in England. The authors determined that implementing routine HLA-A*31:01 testing to mitigate hypersensitivity reactions in patients receiving CBZ for epilepsy is likely to be cost-effective. Their cost-effectiveness model projected decreased cases from 780 to 700 per 10,000 patients, with an incremental cost-effectiveness ratio of £12,808 per quality-adjusted life-year (QALY).[24] Also, Chen et al[25] evaluated the cost and effectiveness of routine HLA-B*15:02 screening to prevent SJS and CBZ-induced toxic epidermal necrolysis in Hong Kong. They reported that HLA-B*15:02 screening is as effective as mammography and pap smears in preventing death in the studied population. In this review, the number of screening tests needed to avoid one case of CBZ-SJS/TEN was 442, and to prevent one end from it was 1474 to 8840.[25] Considering the views of patients and physicians is an essential contribution to understanding preferences for pharmacogenetic testing before starting drug treatments. A study of patient and physician expectations of pharmacogenetic testing before CBZ treatment found that patients would accept a less effective anticonvulsant if the therapy had a lower risk of harm. In comparison, neurologists emphasized the higher negative predictive value for pharmacogenetic testing to reduce the possibility of false negative tests.[26]

If pretreatment testing for HLA-A*31:01 is to be adopted into clinical practice, clinicians must be educated about pharmacogenetic testing. In a study conducted in Hong Kong, HLA-B*15:02 testing led to the unintended consequence of reducing CBZ prescribing from 16.2% to 2.6%, with switching to other AEDs such as phenytoin and LTG; While these drugs were also associated with SJS-TEN. Thus, while the incidence of CBZ-induced SJS-TEN was reduced in those patients tested for HLA-B*15:02, the overall prevalence of SJS-TEN did not change.[27] Patients are advised to stop taking CBZ at the first occurrence of a skin rash, as early discontinuation reduces the risk of progression to more severe disease and death.[15]

In Iran, research has been conducted on this topic,

examining the link between HLA-B1502 and SJS/TEN induced by LTG. Findings suggest that in the Iranian population of Mashhad, the occurrence of SJS/TEN due to LTG is associated with the HLA-B1502 allele.[28] The prevalence of HLA-B*1502 in this study was higher than our study in the population of Tabriz, so the majority of the HLA-B 1502 gene was 5.2% in the low-resolution research, and none of these patients carried the HLA-B 1502 genotype in the high-resolution study. Based on the results obtained in our research, HLA-B 1502 did not show a significant relationship with the incidence of sensitivity caused by LTG consumption.

Mortazavi et al[29] also investigated the relationship between HLAs and drug-induced skin reactions to antiepileptic drugs and antibiotics in the Iranian population. Patients with severe drug side effects (based on clinical and laboratory findings) were subjected to blood sampling and HLA-DNA examination, and the control group included 90 healthy Iranian adults. In this study, HLA-A*31 had a significant relationship only with drug reactions caused by CBZ with eosinophilia and systemic symptoms. At the same time, in the case of LTG, this gene did not show an effective relationship with the occurrence of drug side effects.[29] In our study, HLA-A31:01 did not establish a significant relationship with the incidence of hypersensitivity caused by using CBZ and LTG.

This study of 97 patients failed to find an association between HLA-B*1502 and HLA-A31:01 and skin reactions caused by antiepileptic drugs (CBZ and LTG). This study has limitations that indicate the need for further studies in the future. The first limitation of this study was the low sample size as a single-university study or the existence of this study as a survey in the country's northwestern region, which can provide the basis for future studies in this region.

Conclusion

This study could not find a relationship between HLA-B*1502 and HLA-A31:01 and skin reactions caused by antiepileptic drugs (CBZ and LTG) in the northwest population of Iran. In a more detailed analysis, there was no statistically significant difference between the studied groups in the CBZ subgroup regarding HLA-A31:01. Since all patients with the HLA-A31:01 allele who experienced allergic reactions had been treated with CBZ, this study could not assess the role of HLA-A31:01 in complications associated with LTG. Also, based on the obtained results, HLA-B 1502 did not show a significant relationship with the event of sensitivity caused by the consumption of each CBZ and LTG.

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Authors' Contribution

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Competing Interests

The authors declare there are no conflicts of interest.

Ethical Approval

The study proposal has been approved by the ethics committee of Tabriz University of Medical Sciences with the ethics code IR.TBZMED.REC.1398.696.

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References

1. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet. 1995;345(8948):476-9. doi: 10.1016/s0140-6736(95)90581-2 .
2. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry. 1999;60(2):79-88. doi: 10.4088/jcp.v60n0203.
3. Chung WH, Hung SI. Recent advances in the genetics and immunology of Stevens-Johnson syndrome and toxic epidermal necrosis. J Dermatol Sci. 2012;66(3):190-6. doi: 10.1016/j.jdermsci.2012.04.002.
4. Gillham R, Kane K, Bryant-Comstock L, Brodie MJ. A double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure. Seizure. 2000;9(6):375-9. doi: 10.1053/seiz.2000.0428.
5. Bond CA, Raehl CL. Adverse drug reactions in United States hospitals. Pharmacotherapy. 2006;26(5):601-8. doi: 10.1592/phco.26.5.601.
6. Gibson A, Deshpande P, Campbell CN, Krantz MS, Mukherjee E, Mockenhaupt M, et al. Updates on the immunopathology and genomics of severe cutaneous adverse drug reactions. J Allergy Clin Immunol. 2023;151(2):289-300.e4. doi: 10.1016/j.jaci.2022.12.005.
7. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol. 2012;11(9):792-802. doi: 10.1016/s1474-4422(12)70153-9.
8. Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ. Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. Epilepsy Behav. 2007;10(1):105-10. doi: 10.1016/j.yebeh.2006.08.008.
9. 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(9):885-7. doi: 10.1007/s00228-011-

1009-4.
10. Parveen S, Javed MA. Stevens-Johnson syndrome associated with Lamotrigine. Pak J Med Sci. 2013;29(6):1450-2. doi: 10.12669/pjms.296.4385.
11. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patterns, diagnostic considerations, etiology, and therapeutic management. Semin Cutan Med Surg. 2014;33(1):10-6. doi: 10.12788/j.sder.0058.
12. Wolf R, Wolf D, Davidovici B. In the pursuit of classifying severe cutaneous adverse reactions. Clin Dermatol. 2007;25(3):348-9. doi: 10.1016/j.clindermatol.2007.01.001.
13. Rzany B, Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J, et al. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. J Clin Epidemiol. 1996;49(7):769-73. doi: 10.1016/0895-4356(96)00035-2.
14. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-85. doi: 10.1056/nejm199411103311906.
15. Li Y, Deshpande P, Hertzman RJ, Palubinsky AM, Gibson A, Phillips EJ. Genomic risk factors driving immune-mediated delayed drug hypersensitivity reactions. Front Genet. 2021;12:641905. doi: 10.3389/fgene.2021.641905.
16. Amstutz U, Ross CJ, Castro-Pastrana LI, Rieder MJ, Shear NH, Hayden MR, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Ther. 2013;94(1):142-9. doi: 10.1038/clpt.2013.55.
17. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol. 2013;149(9):1025-32. doi: 10.1001/jamadermatol.2013.4114.
18. Kim BK, Jung JW, Kim TB, Chang YS, Park HS, Moon J, et al. HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population. Ann Allergy Asthma Immunol. 2017;118(5):629-30. doi: 10.1016/j.anai.2017.02.011.
19. 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(2):26-30.
20. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134-43. doi: 10.1056/NEJMoa1013297.
21. 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. doi: 10.1097/FPC.0b013e3282f3ef9c.
22. 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(10):1543-6. doi: 10.2217/14622416.9.10.1543.
23. Yip VL, Pirmohamed M. The HLA-A*31:01 allele: influence on carbamazepine treatment. Pharmgenomics Pers Med. 2017;10:29-38. doi: 10.2147/pgpm.S108598.
24. Plumpton CO, Yip VL, Alfirevic A, Marson AG, Pirmohamed M, Hughes DA. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia. 2015;56(4):556-63. doi: 10.1111/epi.12937.
25. Chen Z, Liew D, Kwan P. Real-world efficiency of pharmacogenetic screening for carbamazepine-induced severe cutaneous adverse reactions. PLoS One. 2014;9(5):e96990. doi: 10.1371/journal.pone.0096990.
26. Powell G, Holmes EA, Plumpton CO, Ring A, Baker GA, Jacoby A, et al. Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and physicians' preferences for testing and service delivery. Br J Clin Pharmacol. 2015;80(5):1149-59. doi: 10.1111/bcp.12715.
27. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology. 2014;83(22):2077-84. doi: 10.1212/wnl.0000000000001034.
28. 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(2):284-7. doi: 10.1111/exd.14240.
29. Mortazavi H, Rostami A, Firooz A, Esmaili N, Ghiasi M, Lajevardi V, et al. Association between human leukocyte antigens and cutaneous adverse drug reactions to antiepileptics and antibiotics in the Iranian population. Dermatol Ther. 2022;35(5):e15393. doi: 10.1111/dth.15393.