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HLA-Related Drug Hypersensitivity Reactions

HLA İlişkili İlaç Aşırı Duyarlılık Reaksiyonları

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ÖZET

İlaç reaksiyonları (İR) iki temel grupta sınıflandırılır. İlki, immünolojik mekanizma aracılı alerjik reaksiyonları; ikincisi, spesifik immünolojik mekanizmanın katılımı olmadan gelişen ilaç aşırı duyarlılık reaksiyonlarıdır (İADR). Morbidite ve mortalite prevalansı İADR'de yüksektir. Bu şiddetli reaksiyonların bazıları spesifik insan lokosit antijen (HLA) alelleri ile bağlantılıdır. Çünkü, HLA genleri genomun en yüksek oranda polimorfik lokuslarını barındırır. Dolayısıyla, İADR etyolojisinde farmakolojik doz etkisinden ziyade genetik yatkınlık farmokogenetik araştırmaların son dönem merak uyandıran alanlarından birini oluşturmaktadır. İADR ile spesifik HLA ilişkileri coğrafi bölgeler ve etnik gruplar arasında farklılık gösterebilir. Aynı populasyonun bireyleri arasında dahi HLA allellerine göre ilaç yanıtı ve duyarlılığı farklılık teşkil edebilir. Çok sayıda çalışma, spesifik HLA alellerinin İADR geliştirme riskini artırdığına dair kanıtlar sağlamıştır. Çünkü, ilaca yanıt veren T hücresi aktivasyonunda HLA, ilaçlar ve T hücresi reseptörleri arasındaki etkileşim HLA allellerine göre değişebilmektedir. Allel türüne göre, T hücresinin aktivasyonu, antijen ile etkileşimi doğurduğu immün cevap farklılığı doğuran en önemli moleküler sistemdir. Bu özellikler HLA allerinin İADR üzerinden farmakogenetik ilişkisini ortaya koyarken, farmakokinetik etki içinde HLA allel çeşitlerine göre ilacı hızlı metabolize eden veya hiç metabolize etmeden toksik yanıt geliştiren bireyler de olabilir. Bu doğrultuda, toplumlarda farmakogenomik ilişkilerin incelenmesi, HLA alleleri ile ilaç duyarlılığı için yeni verilerin keşfedilmesi, kanıt oranıyla bulunanların doğrulanması hem ilaç yararlanımı için sağlık kalitesi üzerinden hem de maliyet etkinliği üzerinden büyük fayda sağlayacaktır. İlaç kullanımından önce HLA kimliklendirmesi ile kişiye özel farmakolojik tedavi, gelişen toplumlarda güncel tedavi hedeflerinin başında gelmektedir. Bu derlemede, ilaç aşırı duyarlılık reaksiyonlarına yol açan modeller, en sık reaksiyon veren ilaçlar, ilişkili HLA alleleri ve izlenen klinik tablolar araştırılmıştır.

Anahtar Kelimeler: HLA, ilaç, aşırı duyarlılık reaksiyonları

ABSTRACT

Drug reactions (DR) are grouped into two basic classes. Allergic reactions through by immunological mechanisms is one of them; the second is the drug hypersensitivity reactions (DHR) that occur without the engagment of a specific immunological response. Prevelance of DHR is a extensive cause of morbidity and mortality. These severe reactions are originated from specific human leukocyte antigen (HLA) alleles. Since, HLA genes include the high rate of polymorphic loci in the genome significantly. Thus, genetic predisposition rather than the pharmacological dose effect in the etiology of DHR account for one of the most intriguing sites of pharmacogenetic research. Specific HLA associations with DHR may be varry between geographic regions and ethnic groups. Even among individuals of the same population, drug response and sensitivity may differ according as HLA alleles. Numerous investigations have provided evidence that some of HLA's increase the risk of growing DHR. In view of the fact that the interconnection between HLA, drugs and T cell receptors in drug-responsive T cell reaction may vary widely depending on HLA alleles. According to, the allele type, the activation of the T cell and its interaction with the antigen is the most significant molecular system that causes variations in the immune response. While these features reveal the didtinctive genetic relationship of HLA alleles through DHR, there may be individuals who metabolize the drug rapidly or develop a toxic response without metabolizing it at according to HLA allele types within the pharmacokinetic effect. In this line, determining pharmacogenomic datas in societies, discovering new evidence for HLA alleles and drug sensitivity, and verifying the findings with the evidence rate will provide great benefits both in terms of health quality for drug use and cost effectiveness. Personalized pharmacological treatment with HLA identification before drug use is one of the current treatment targets in developing countries. In this review, the models that cause drug hypersensitivity reactions, the most frequently reacting drugs, the associated HLA alleles and the clinical presentations were investigated.

Keywords: HLA, drug, hypersensitivity reactions

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INTRODUCTION

OIn the region of the Major Histocompatibility Complex (MHC) of the human genome, HLA class I and class II loci are located. HLA genes are highly polymorphic about 8000 functional HLA-A/B/C alleles and 3000 HLA-DR/DQ/DP alleles (1). Drug hypersensitivity reaction (DHR) is explained by the World Health Organization (WHO) as "a harmful and undesirable answer to normal doses of a drug used for the prophylaxis, diagnosis or treatment of disease". While most DHRs are considered predictable (type A) based on the known pharmacologic effect of the drug, immune responses caused by a smaller number of drugs are generally considered unpredictable (type B) and dose most polymorphisms are located in the antigen-binding cleft peptide binding region. The purpose of HLA genes are to provide the antigens produced by HLA class I or to present peptides stem from on the cell surface HLA class II for immune system. These peptides are recognized by circulating T cells via T cell receptors (TCRs). Since antigen-MHC association is responsible for the formation of pharmacologic adverse reactions, HLA genotype is an important risk factor in drug reactions (2).

A drug hypersensitivity reaction is defined as "a harmful and undesired response to normal doses of a drug used for the prophylaxis, diagnosis or treatment of a disease" by the WHO. Most DHRs are accepted as predictable (type A) sourced from pharmacological interconnection of the drug, while immune responses caused by a smaller number of drugs are generally considered unpredictable (type B) and independent of dose (3). Type B reactions constitute only about 13% of DHRs and are more severe than the type A reactions. A subtype B of DHR is T cell-mediated drug hypersensitivity. T cell-mediated reactions are characterized by systemic reactions (drug-induced hypersensitivity sNGSrome) and skin reactions. These reactions occur after 3-4 days of drug remedy and sometimes longer >30 days. Consistent with removal of antigen, symptoms decrease with discontinuation of drug treatment; but, represent of the drug may be fatal, owing to rapid activation of a memory T cell population (4). Studies considering the role of HLA alleles triggiered T cell have revealed corporations between DHRs and polymorphic HLA alleles. The association between DHRs and HLA class I-II alleles in some ethnic communities has been clearly established. There are also strong associations between DHR and genetic polymorphisms of some enzymes that metabolize drugs. In this compilation, the models leading to drug hypersensitivity reactions, the associated HLA alleles and the clinical pictures observed are reviewed.

1.Models Leading to Drug Hypersensitivity Reactions

Reactions developed with HLA alleles are T cell-mediated Type IV delayed-type reactions. It is not defined drug-mediated T cell activation yet so, different models have been proposed. According to these models, HLA genes give out drugs to TCRs in three different ways (figure 1).

Hapten model has been demostrated that the drug has an irreversible covalent bond with the peptide. Drug-modified peptides are generated. These drug-modified peptides are then presented to TCRs by HLA molecules (5). The second mechanism is hold on the pharmacologic interconnection with immunity (P-I). The drug links directly with HLA complexes in a non-covalent bond here to trigger activation. Since the drug interconnets with peptides on the surface of cell presented by HLA in the P-I model, it does not depend on intracellular protein processing mechanism. Theoretically, the drug first triggers the T cell by interacting with HLA or TCRs. However, both scenarios involve the formation of a drug-peptide HLA-TCR complex. In both models, TCRs receive binding signals from HLA, peptide and drug, the only difference is in the nature of the binding of the drug molecule with HLA (6). The third mechanism is the modified peptide repertoire model. There is a non-covalent interaction between the drug and the HLA molecule. The drug interacts with the antigen binding cleft of the HLA molecule instead of interacting at the -TCR interface. It

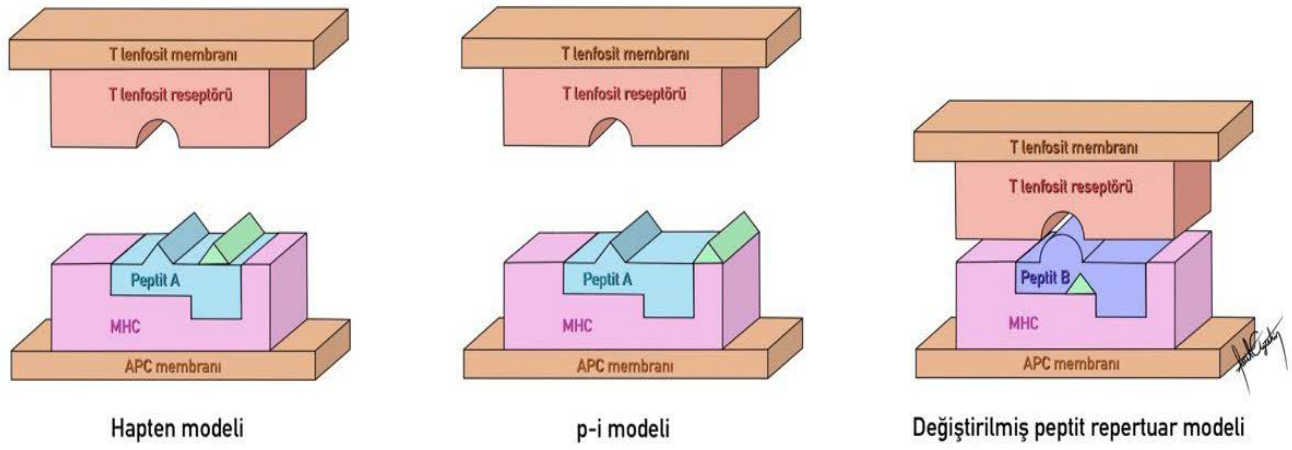

Figure 1. Drug presentation patterns of HLA molecules to the TCR (Figure is created by Mehmet Fatih Aytekin)

occupies some part of the space available for peptide binding. It changes the peptide binding preferences and peptit binding motif of the HLA molecule while doing this. The emerged HLA-drug-peptide complexes are conformationally different from the constitutive HLA-peptide complexes and are recognized as unfamiliar by circulating T cells (7).

Figures show drug presentation of HLA alleles in the MHC region to the TCR. *The green pyramid symbolizes the drug.

2.Clinical Consequences of Drug Hypersensitivity Reactions

HLA antigens vary according to individual, race, community and disease. The relationship between HLA class I and II alleles and drug allergy is specific to drug, phenotype (clinical picture) and ethnicity. The most important HLA-ADR associations found in studies conducted in the last 10 years are as follows (table 1).

2.1. Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (Ten)

Stevens Johnson Syndrome characterized by acute, rare and potentially fatal skin reactions involving loss of skin and by systemic symptoms. In more than 80 percent of cases, drugs are the triggering factor. SJS is less common but unpredictable reaction for DHR involving drug-specific CD8+ cytotoxic lymphocytes, the Fas-Fas ligand (FasL) pathway, and the tumor necrosis factor-alpha (TNF) pathway. Clinically, these two manifestations are distinguished from each other by examining body surface area: it is defined as SJS if there is less than 10% skin damage, TEN if there is more than 30% epidermal detachment, and SJS-TEN if there are skin problems between 10% and 30% (8).

2.2. Drug-induced Hypersensitivity Syndrome (DIHS)/Drug Reaction Syndrome with Eosinopophilia and Systemic Symptoms (DRESS)

DRESS is a rare T cell-mediated delayed-type drug hypersensitivity reaction that is serious and potentially fatal. It is more common in adults. The syndrome affects not only the skin but also other organs such as the liver, kidneys and heart. The "R" in the acronym DRESS, which previously stood for "rash", was later changed to "reaction". The mortality rate is approximately 10%, depending on the age of the patient, underlying comorbidities and the drug involved. Typically occurs in two weeks or two months after starting a medicine. It characteristically occurs with fever, widespread rash, lymphadenopathy, hematologic abnormalities and involvement of one or more internal organs (9).

2.3. Maculopapular Exanthema (MPE)

It is a frequently observed drug-induced cutaneous hypersensitivity with a favorable outcome. It is a T cell-mediated reaction. It occurs within 1 week after the initiation of the causative drug use and regresses in 7-14 days. It usually has a mild course and is observed in generalized form less frequently (10).

2.4. Drug-Induced Liver Injury (DILI)

Drug-Induced Lıver Injury (DILI) has been the most significant source of acute liver failure. It is an important but rare side effect that can range from asymptomatic elevation in liver tests to acute liver failure, transplantation or death. DILI has classically been categorized as direct dose-dependent or idiosyncratic, but indirect injury has emerged as the third type of drug-induced liver injury. Idiosyncratic DILI cannot be predicted (11).

2.5. Agranulocytosis

It is a rarely seen, potentially life-threatening state. It can be attributed to drugs in >70% of cases. In agranulocytosis, the peripheral neutrophil count is < 0.5 x 10 9. It often presents with a severe sore throat, but isolated fever, pneumonia or septicemia are not uncommon

3. HLA Alleles Associated with Drug Hypersensitivity Reactions

Well-known drugs associated with HLA alleles causing drug hypersensitivity reactions are given in table 1. Data of pharmacogenomics including HLA alleles are regularly updated and available on the 'Pharmacogenomics Knowledge Base' with significant evidence (13). Prominent drug-HLA- DHR associations are described below.

3.1. Abacavir

Abacavir-induced hypersensitivity reaction develops against HIV-1 remedy. Fever, common rash, fatigue, gastrointestinal symptoms and shortness of breath are observed. It has been reported that HLA-B*57:01 carrying was a significant risk abacavir-induced hypersensitivity syndrome (14). According to predict 1 and shape studies that patients with HLA-B*57:01 carriage should not use abacavir. (15,16). The FDA has issued a package insert warning for abacavir stating that "HLA-B*57:01 detecting should be performed in all patients before abacavir is started for the first time or given again, with or without prior allelic detecting" (17). HLA-B*57:01 related with abacavir-induced hypersensitivity at about %3 in Middle Eastern. The prevalence of the allele in Caucasian race, African-Americans and Thai populations is approximately 6%. It is 2% and 4%, respectively (18) In Chinese and Koreans.

3.2. Carbamazepine

Carbamazepıne is used for epilepsy treatment, bipolar disorder and the other neurological disorders. SJS/TEN, maculopapular exanthema and DRESS reactions have been reported following carbamazepine treatment (19). People carriying HLA-B*15:02 have been risk with SJS/TEN (20). It is important to note that not all patients with carbamazepine-associated SJS/TEN reactions carried the HLA-B*15:02 allele. In recent studies carbamazepine-SJS/TEN have been assosiated with HLA-B*15:21, HLA-B*15:11 and HLA-B*15:08 genotypes (20,21). DRESS/DIHS observed with carbamazepine usage is not related with HLA-B*15:02. Carbamazepine-induced immunity related drug reactions and HLA-A*31:01 allele has been associated in Chinese, Northern European, Japanese and Korean origin (22). The US Food and Drug Administration (FDA) states on its website that HLA B*15:02 allele scanning should be performed before starting carbamazepine in high-risk groups (people of Southeast Asian origin) and if positive, the drug should not be started. It is also recommended to avoid all aromatic antiepileptic drugs in HLA B*15:02 positive individuals (23).

The prevalence of HLA-A*31:01 in Caucasians and Asians was found to be high as another allele associated with carbamazepine cutaneous adverse reactions (24). In another study, it was found evidince between HLA-A*31:01 and carbamazepine. Whereas the HLA-A*02:01 allele is associated with an significant risk triggired by carbamazepine and lamotrigine with maculopapular exanthema (25,26).

3.3. Phenytoin

Phenytoin is used for epileptic remedy has been related with severe cutaneous effect including SJS/TEN, DRESS and maculopapular eruption as well. HLA-B*13:01, HLA-B*15:02 and HLA-B*51:01 carriage have been risk factor for the treatment of phenytoin. In an investigation further, phenytoin-SJS/TEN was reported to be associated with HLA-B*15:02 carriers (27-30). It was identified that severe skin reactions caused by phenytoin were significantly related with CYP2C9*3 carried. In a study, in which combined displaying was done for detecting CYP2C9 variants and HLA-B*15:02 carriage, it was shown that the sensitivity of phenytoin-SJS/TEN was 62.5% in combination (20).

3.4. Allopurinol

Allopurinol is used against hyperuricemia and gout. The variable in approximately 2% of patients starting treatment, is responsible for a drug sensivity reaction primarily of cutaneous phenotype. In 2005, the HLA-B*58:01 genotype was shown to be related with allopurinol-trigered SJS/TEN and DRESS in Han Chinese individual descent. It has been similar association in Thai, Korean and Japanese populations (29).

HLA-B*58:01 is estimated to be responsible for almost 50% of allopurinol-induced adverse effect in European and Japanese people. It is thought to be a dose-dependent reaction (19). A very strong HLA -DHR association between HLA B*58:01 and allopurinol-associated SJS/TEN has been demonstrated in different populations. Besides, HLA-A*33:03, which is significantly found in Europeans for allopurinol. HLA-C*03:02 is another allele that has been shown to be associated (9).

3.5. Nevirapine

In recent years, HLA-C*04:01 was significantly associated with an increased risk of cutaneous reactions and hepatotoxicity hypersensitivity to nevirapine is an antiretroviral. Black Africans, Caucasians and Thais populations can be ranged from 8% to 14% or even higher in the Iranian-Baluch population, where it can be 28%. HLA-B*35:01 and HLA-DRB1*01:01 are associated with nevirapine hypersensitivity as well (31).

3.6. Lapatinib

Lapatinib is a therapeutic drug used for breast cancer and carrier of -DRB1*07:01 have been found increased risk in patients treated with lapatinib. These HLA alleles are present by 15-25% of Caucasian, Asian, African and Hispanic indivudials and the risk have been found more less in Japanese. Prevalence can range from 10% to 25% in GME. Accoring to FDA lapatinib drug label is that liver can be adviced by monitoring for lapatinib treatment, irrespective of HLA allelles (32).

3.7. Aspirin

Using of aspirin and carried of HLA-DPB1*03:01 have been found significant risk by 15% in Sudanese and Tunisians with asthma. It was found an associations in the White Polish inviduals and Koreans. However, studies will be needed to validate the findings of the HLA-DPB1*03:01 allele in different populations (32,33).

4. Methods Used for Detection of HLA Alleles

Since the association between HLA alleles and developing DHR has been shown in many studies, genetic testing for determining HLA alleles is very important for new users of the above drugs. Haplotype results are either "positive" HLA-B*57:01 is detect in one or both copies of the HLA-B gene or "negative" no copies of HLA-B*57:01 are detect. Since HLA genes are expressed in a codominant manner, there are no intermediate phenotypes. Although most of the technologies have been developed to detect the HLA-B*57:01 allele, one of the first prominent alleles identified, tests can also be applied to test for other alleles (34). Several techniques are available for HLA genotyping methods.

5. DNA-Related Molecular Genetic Tests

DNA sequence-specific primers (SSP), sequence-specific oligonucleotides (SSO), real-time polymerase chain reaction (real-time PCR), Sanger and next generation sequencing (NGS/Next generation sequencing-NGS) are all DNA-related molecular genetic methods. DNA based HLA types amplified by PCR are common laboratory procedures. PCR amplification of DNA is used as a means of enriching a selected DNA region. Different methods are used for HLA typing after this stage; SSP (sequence specific primer), SSO (sequence specific oligonucleotide), RFLP (restriction fragment length polymorphism) and reverse SSOP dot blot technologies (33).

Fortyping,HLA-SSOusessequence-specificoligonucleotides (SSOs) to determine which HLA alleles are present in a sample that has been amplified by using biotin-labeled primers in PCR. It is the sequence-specific oligonucleotide-hybridization probes used following amplification that provide specificity. Microbead and fluorescence detection technology have been combined with an automated software technique in SSO which is made with Luminex. For each locus, an array of microspheres is used, which can be recognized by their specific color resulting from two internal fluorescent dyes. Each microbead is combined with a single probe capable of hybridization with a biotin-labeled complementary amplicon. When hybridization occurs, fluorescence signal ,stemming from the fluorescent (streptavidin-PE)-labeled amplicons captured by the beads, can be quantified by measuring. That is, all SSOs are analyzed at the same time. Luminex and Auto-Lipa devices can also be studied on a gel basis. It is a low resolution method.

HLA-SSP is a method in which only the desired alleles are amplified with specific primers. Exactly matched primers are used. The amplified PCR product is processed by agarose gel electrophoresis. The image obtained following the electrophoresis process is evaluated as 'Score' by means of various software. HLA-SSOP dot blot; DNA amplified with PCR is passed on the membrane by dot technique. The probes on the membrane are subjected to DNA for hybridization, then

the membranes are washed very well. Hybridization of the probe indicates the presence of target HLA antigens (35).

Restriction fragment length polymorphism (RFLP) is a method that is no longer used today. Alleles can also be detected by sequencing methods after PCR. These tests are high resolution. Sanger sequencing and new generation sequencing methods are used. Due to its accuracy, high throughput and speed, NGS is increasingly becoming the preferred method for HLA typing. The most important benefit of NGS is that it eliminates ambiguities at a cost comparable to Sanger sequencing and without the need for additional screens. The international ImMunoGeneTics project/human leukocyte antigen (IMGT/HLA) database is actively used in the variant calling process of NGS. The use of flow cytometry-monoclonal antibody and patch testing are tests that are not performed with PCR and DNA.

CONCLUSION

HLA-ADR pharmacogenomic relationships are not a well-studied area in our country. The daily use of next-generation sequencing and bioinformatic algorithms developed for HLA genotyping will soon provide an opportunity to reduce the information gap in this field in countries around the world. In the near future, new HLA-related pharmacogenomic markers will be identified, especially in populations where genomic projects are ongoing. Revealing the pharmacogenomic HLA profiles of countries will play an important role in reducing drug-related side effects. Polimorphism of HLA allelles especially due to ethnic origin should motivate HLA-related investigations in different populations. As a result of the data obtained, scanning the relevant HLA allele before the drug usage will be important for cost-effectiveness evaluation.

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REFERENCES

1. Robinson J, Halliwell JA, Hayhurst JD, et al. The IPD and IMGT/HLA database: allele variant databases. Nucleic Acids Res 2015;43:423-31.
2. Reche PA, Reinherz EL. Sequence variability analysis of human class I and class II MHC molecules: Functional and structural correlates of amino acid polymorphisms. J Mol Biol 2003;331(3):623-41.
3. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003;139(8):683-93.
4. Pichler W, Yawalkar N, Schmid S, et al. Pathogenesis of drug-induced exanthems. Allergy 2002;57(10):884-93.
5. Jaruthamsophon K, Thomson PJ, Sukasem C, et al. HLA Allele-Restricted Immune- Mediated Adverse Drug Reactions: Framework for Genetic Prediction. Annu Rev Pharmacol Toxicol 2022;62:509-29.
6. Britschgi M, von Greyerz S, Burkhart C, et al. Molecular aspects of drug recognition by specific T cells. Curr. Drug Targets 2003;4(1):1-11.
7. Pompeu YA, Stewart JD, Mallal S, et al. The structural basis of HLA associated drug hypersensitivity syndromes. Immunol. Rev. 2012;250(1):158-66.
8. Shanbhag SS, Koduri MA, Kannabiran C, et al. Genetic Markers for Stevens- Johnson Syndrome/Toxic Epidermal Necrolysis in the Asian Indian Population: Implications on Prevention. Front Genet 2021;12;11:607532.
9. Stirton H, Shear NH, Dodiuk-Gad RP. Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS)/Drug-Induced Hypersensitivity Syndrome (DiHS)-Readdressing the DReSS. Biomedicines 2022;26;10(5):999.
10. Björnsson HK, Björnsson ES. Drug-induced liver injury: Pathogenesis, epidemiology, clinical features, and practical management. Eur J Intern Med 2022;97:26-31.
11. Garbe E. Non-chemotherapy drug-induced agranulocytosis. Expert Opin Drug Saf 2007;6(3):323-35.
12. Whirl-Carrillo M, McDonagh EM, Hebert JM et al. Pharmacogenomics knowledge for personalized medicine. Clin. Pharmacol 2012;92(4):414-7.
13. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359(9312):1121-2.
14. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358(6):568-79.
15. Mallal S, Nolan D, Witt 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.
16. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46(7):1111-8.
17. Çelik G, Dursun B. 16. Türkiye Ulusal Allerji ve Klinik İmmünoloji Derneği.(eds). İlaç aşırı duyarlılık reaksiyonlarına yaklaşım ulusal rehber güncellemesi. Buluş Tasarım, Ankara, 2019.
18. Masmoudi HC, Afify N, Alnaqbi H, et al. HLA pharmacogenetic markers of drug hypersensitivity from the perspective of the populations of the Greater Middle East. Pharmacogenomics 2022;23(12):695-708.
19. White KD, Chung WH, Hung SI, et al. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: The role of host, pathogens, and drug response. J Allergy Clin Immunol 2015;136(2):219-34.
20. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens- Johnson syndrome. Nature 2004;428(6982):486.
21. Mehta TY, Prajapati LM, Mittal B, et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol 2009;75(6):579-82.
22. Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia 2010;51(12):2461-65.
23. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine- induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134-43.

24. Grover S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet. Genomics 2014;24(2):94-112.
25. Ksouda K, Affes H, Mahfoudh N, et al. HLA-A*31:01 and carbamazepine-induced DRESS syndrom in a sample of North African population. Seizure 2017;53:42–6.
26. Li LJ, Hu FY, Wu XT, et al. Predictive markers for carbamazepine and lamotrigine-induced maculopapular exanthema in Han Chinese. Epilepsy Res 2013;106(1-2):296-300.
27. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007;48(5):1015-8.
28. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA. 2005;15;102(11):4134-9.
29. Cristallo AF, Schroeder J, Citterio A, 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(4):303-9.
30. Cornejo Castro EM, Carr DF, et al. HLA-allelotype associations with nevirapine-induced hypersensitivity reactions and hepatotoxicity: A systematic review of the literature and meta analysis. Pharmacogenet Genomics 2015;25(4):186-98.
31. Dekker JW, Nizankowska E, Schmitz-Schumann M, et al. Aspirin-induced asthma and HLA-DRB1 and HLA-DPB1 genotypes. Clin. Exp. Allergy 1997;27(5):574–7.
32. Tangamornsuksan W, Kongkaew C, Scholfield CN, et al. HLA-DRB1*07:01 and lapatinib-induced hepatotoxicity: A systematic review and meta- analysis. Pharmacogenomics J. 2020;20(1):47-56.
33. Choi JH, Lee KW, Oh HB, et al. HLA association in aspirin-intolerant asthma: DPB1*0301 as a strong marker in a Korean population. J Allergy Clin. Immunol 2004;113(3):562–4.
34. Fan WL, Shiao MS, Hui RC, et al. HLA Association with Drug-Induced Adverse Reactions. J Immunol Res 2017;2017:3186328.
35. Bunce M, Passey B. HLA typing by sequence-specific primers. Methods Mol Biol. 2013;1034:147-59.