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A Review of HLA Genes in Pharmacogenetics: Risk Assessment of Adverse Drug Reactions

Shinae Yu

Department of Laboratory Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Adverse drug reactions (ADRs) is a hypersensitivity reactions to specific medications, and remain a common and major problem in healthcare. ADRs suchc as drug-induced liver injury and life-threatening severe cutaneous adverse drug reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms can be occurred by uncontrolled expansion of oligoclonal T cells according to genetically predisposing *HLA*. In this review, I summarized the alleles of *HLA* genes which have been proposed to have association with ADRs caused by different drugs.

Key words: HLA, Pharmacogenetics, Adverse drug reaction

REVIEW ARTICLE

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Correspondence to: Shinae Yu
Department of Laboratory Medicine, Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeun-daero, Haeundae-gu, Busan 48108, Republic of Korea
Tel: +82-51-797-3189
Fax: +82-51-797-3194
E-mail: tlsdo55@paik.ac.kr

ORCID
Shinae Yu: https://orcid.org/0000-0002-9527-5853

INTRODUCTION

The human leukocyte antigen (HLA) is synonymous with the human major histocompatibility complex (MHC), a term used to describe a group of genes in animals and humans that encode a variety of cell surface markers, antigen-presenting molecules, and other proteins involved in immune function [1]. The classical MHC spans 3.6 megabases and comprises more than 200 genes, including many immune system genes on the short arm of chromosome six at position 6p21.3, and has been subdivided into three regions: class I, class II, and class III [2]. *HLA* genes are included in class I and II of MHC regions. The class I region contains the genes encoding the "classical" class I HLA antigens: HLA-A, B, and C. Class I antigens are expressed on almost all cells of the body, except erythrocytes and trophoblasts, at varying density [3]. The class II region contains the genes encoding the HLA class II molecules, HLA-DP, DQ, and DR. Class II molecules are constitutively expressed on antigen-presenting cells such as dendritic cells, macrophages, or B cells, and can be induced during inflammation on many other cell types that normally have little or no expression [4,5].

The *HLA* genes have been studied in several medical interests. First, typing, and eventually matching, of donors and recipients in both solid organ and hematopoietic stem cell transplantations are important elements in transplant outcome [6,7]. Second, several diseases is associated with *HLA* genes such as ankylosing spondylitis with *HLA-B27*, Behçet disease with *HLA-B51*, celiac disease with *HLA-DQ2* and *DQ8*, narcolepsy with *HLA-DQB1*06:02*, and rheumatoid arthritis with *HLA-DR4*. Lastly, there are multiple instances of associations between HLA alleles, mostly class I, and hypersensitivity reactions to specific medications, known as adverse drug reactions (ADRs) [8]. Data on a variety of drugs and severe drug allergies demonstrated that certain *HLA-B* alleles represent highly significant risk factors for severe side effects to a particular drug and are also involved in present-

ing the drug to the immune system [9-11]. In this review, we focus the current findings on genetically predisposing *HLA* genetic markers for risk assessment of ADRs.

ADRS BASED ON IMMUNOLOGIC MECHANISM

ADR is a general term referring to any untoward reaction to a medication, and may be broadly divided into two types, type A and type B. Type A can affect any individual, given sufficient dose and exposure, and are predictable from the known pharmacologic properties of a drug, while type B represents drug hypersensitivity reactions (DHRs) mediated by immunologic and/or inflammatory mechanism, and occur in a susceptible subgroup of patients [12].

Immunologic reactions have been divided into four categories (I to IV) according to the Gell and Coombs system [13]. Among them, type IV reaction involves the activation and expansion of T cells by different HLA alleles, and is a delayed-type hypersensitivity which requires time from many hours to days after drug exposure. This type of ADRs can take many different forms, which vary in significance from inconvenient to life threatening. Uncontrolled expansion of oligoclonal T cells that have been massively stimulated by the drug can cause drug-induced liver injury (DILI) and life-threatening severe cutaneous adverse drug reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS). These ADRs are the most dangerous of the delayed DHRs, often appear after weeks of uncomplicated treatment, at which point patients suddenly develop signs and symptoms of a fulminant immune reaction [14].

Drugs or its reactive metabolites are considered as foreign antigens that bind to T cell receptors (TCR) and further activate immune response. Four hypotheses have been proposed to explain how the immune system is activated in a HLA molecule-dependent manner: the "hapten/prohapten" theory; the pharmacologic interaction of drugs with immune receptors (p-i); the "altered peptide repertoire" model; and the "altered TCR repertoire" model [14-16]. Among these theories, the p-i concept proposes that some drugs can interact directly with certain TCRs or HLA molecules that are not their primary therapeutic targets. In the p-i, the drug interacts with a highly complex and polymorphic receptor system. The ability of drugs to bind to some of these immune receptors varies enormously between different individuals and depends on the immunogenetic background. This explains why many of the severe drug hypersensitivity reactions due to p-i mechanism occur in carriers of certain *HLA* alleles [17].

ADRS AND HLA ALLELES

Immune-mediated ADRs have been reported to be observed in specific ethnic groups and to be associated with *HLA* alleles [18]. Genome-wide association study and case–control candidate gene study are two main approaches that are implemented when trying to determine the genetic components of *HLA* associated ADRs, and have helped to identify *HLA* alleles associated with increased risk of developing ADRs [9,19-21]. It has been reported that *HLA* associated ADRs have huge racial variability in the frequency of *HLA* alleles and serious problems [9, 22,23]. Ghattaoraya et al. [24] have designed and implemented a relational database and created webpages called the HLA-ADR (http://www.allelefrequencies.net/hla-adr) through systematic review of the literature for *HLA* associated ADRs and semi-automated literature mining. It provides clinicians and researchers with a up to date centralized resource from which to investigate *HLA* associated ADRs for approximately 50 kinds of drugs including antibiotics, antiepileptic, and antiviral drugs. Users can query the database via the use of filters such as genes/alleles, drugs, patient ethnicity and the country/region where the study was conducted. In this section, I would like to summarize four drugs that are particularly well known among the many drugs that cause *HLA*-related ADR: Avakabir, carbamazepine, alopurinol and fluoroacillin.

Abacavir and HLA-B*57:01

Abacavir is a commonly used guanosine nucleoside analogue with potent antiviral activity against human immunodeficiency virus (HIV). About 5% of treated patients, abacavir can develop hypersensitivity responses characterised by multisystem involvement that can be fatal in rare cases. Symptoms usually appear within the first 6 weeks of treatment and include fever, rash, lethargy, malaise, headache, paraesthesia, edema, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory symptoms such as cough, dyspnea, or pharyngitis [25]. In very rare cases, abacavir might result in more severe reaction such as SJS/TEN [26, 27]. The current diagnostic approach to abacavir hypersensitivity is based on clinical diagnosis and the presentation of multiple symptoms and signs compatible with abacavir hypersensitivity, as there is no diagnostic test that has been shown to

have 100% sensitivity.

The association between abacavir hypersensitivity and *HLA-B*57:01*, *HLA-DRB1*07*, and *HLA-DQB1*03* was first reported in 2002, and *HLA-B*57:01* among these HLA alleles was present in 14 (78%) of the 18 patients with abacavir hypersensitivity and in 4 (2%) of the 167 abacavir-tolerant patients [28]. Immediately after this report, case-control study of mainly white HIV-infected men, *HLA-B*57:01* was present in 39 (46%) of 84 patients clinically diagnosed with abacavir hypersensitivity versus 4 (4%) of 113 controls [29]. Several studies, even after that, have shown that *HLA B*57:01* is most strongly associated with abacavir hypersensitivity [30-35].

*HLA-B*57:01* is useful as a genetic screening test before abacavir is prescribed, and all patients should be screened for *HLA-B*57:01* prior to abacavir therapy. Screening for *HLA-B*57:01* represents a major advance in the care of HIV-infected patients and remains the mainstay in preventing abacavir hypersensitivity and its associated morbidity and mortality [36].

Allopurinol and HLA-B*58:01

Allopurinol is a xanthine oxidase inhibitor used in the treatment of hyperuricemia-related diseases, such as gout, Lesch–Nyhan syndrome, and recurrent urate kidney stones [37]. The range of allopurinol hypersensitivity varies from mild with maculopapular eruption (MPE) to SCARs including SJS/TEN, DRESS, and the potentially life-threatening systemic manifestation. Allopurinol is one of the most frequent causes of ADRs, accounting for 5% of all cases of SCARs [38]. In allopurinol hypersensitivity, impaired renal function and increased plasma levels of oxypurinol and granulysin correlated with the poor prognosis of allopurinol-induced SCARs [39]. A skin rash may be followed by more severe hypersensitivity reactions, hence allopurinol should discontinue at first sign of skin rash or other signs indicative of allergic reaction.

The association between allopurinol-induced SCARs and *HLA-B*58:01* was first reported in 2005, and *HLA-B*58:01* was present in 51 (100%) of the 51 patients with allopurinol-induced SCARs and in 20 (15%) of the 153 allopurinol-tolerant patients [40]. Several studies, have validated that *HLA B*58:01* is associated with allopurinol-induced SCARs in different ethnic populations such as European [41], Japanese [42,43], Thai [44,45], Korean [46,47], Caucasian [48,49], and Han Chinese [50-53]. It is considered that *HLA-B*58:01* testing prior to initiation of therapy in patients at elevated risk for SCARs [54], and it should be avoid allopurinol in any patient testing positive for the allele.

Carbamazepine and HLA-B*15:02

Carbamazepine is an effective drug used in the treatment of epilepsy, trigeminal neuralgia, and acute manic and mixed episodes in bipolar I disorder. Carbamazepine hypersensitivity reactions include SJS/TEN, MPE, DRESS and systemic symptoms due to multiorgan hypersensitivity. These reactions are estimated to occur in 1 to 6 per 10,000 new patients on carbamazepine in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Up to 90% of patients experience carbamazepine hypersensitivity reactions within the first few months of treatment [55].

The association between carbamazepine-induced SCARs and *HLA-B*15:02* was first reported in 2004, and *HLA-B*15:02* was present in 44 (100%) of the 44 patients with carbamazepine -induced SJS and in 3 (3%) of the 101 carbamazepine -tolerant patients [9]. Studies in Han Chinese have found a strong association between the risk of developing SJS/TEN and the presence of *HLA-B*15:02* which is found almost exclusively in patients with ancestry across broad areas of Asia [9,56-58]. Therefore patients with ancestry in genetically at-risk populations (Han Chinese, Thai, Malaysian, Indian, or Vietnamese descent) should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine, and patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk [59].

Flucloxacillin and HLA-B*57:01

Flucloxacillin is an antibiotic belonging to penicillin class and is used widely for the treatment for staphylococcal infection in Europe. Flucloxacillin is one of the triggers of DILI and is also reported to be associated with prolonged damage leads to the loss of bile ducts and overt ductopenia [60].

The association between flucloxacillin-induced DILI and *HLA-B*57:01* was proved by genome-wide association study, and *HLA-B*57:01* was present in 43 (84%) of the 51 patients with flucloxacillin-induced DILI and in 4 (6%) of the 64 flucloxacillin-tolerant patients [61]. The top SNP associated with flucloxacillin DILI in this study was rs2395029 which is a missense polymorphism in the *HCP5* gene which was previously found to be in complete linkage disequilibrium with *HLA-B*57:01* in subjects of European origin [62]. Flucloxacillin has been proven to stimulate cytotoxic T cells in two distinct manners; One is a hapten mechanism, and the other is p-i-based T cell reactivity which was restricted to the *HLA-B*57:01* allele [63]. It means that the presence of *HLA-B*57:01* developes

DILI due to drive cytotoxic T cell responses to the penicillin-derivative flucloxacillin toward not a hapten mechanism but p-i concept. Therefore screening for *HLA-B*57:01* prior to flucloxacillin therapy is useful in order to prevent DILI.

CONCLUSION

In this review, I summarize the *HLA* alleles associated with ADRs induced by different drugs. The immune reactions to four drugs reviewed, abacavir, carbamazepine, allopurinol, and flucloxacillin, occur if the *HLA* is present, with a NPV of approximately 100% [17]. This high NPV means that the particular *HLA* allele is required for the immune reaction to occur. In vitro analysis revealed that these *HLA*-linked immune reactions are due to p-i *HLA* reactions and explain the association by the availability of a suitable binding site in the involved *HLA* protein [18,64]. However, the same drugs can also cause milder reactions such as rashes, which are not *HLA*-linked but may occur via a hapten mechanism.

Recommendations have been made for screening patients for specific alleles prior to administration of drugs such as abacavir, carbamazepine, allopurinol, and flucloxacillin [65]. Therefore patients should be confirmed for *HLA-B* genotyping prior to initiating treatment with these drugs, and once a patient has been identified as having a high-risk *HLA* allele, family members of that patient should also be advised to avoid the relevant drug, as familial occurrence of such DHRs has been noted.

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