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Studies on abacavir-induced hypersensitivity reaction: a successful example of translation of pharmacogenetics to personalized medicine

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Abacavir is an effective nucleoside analog reverse transcriptase inhibitor used to treat human immunodeficiency virus (HIV) infected patients. Its main side effect is hypersensitivity reaction (HSR). The incidence of the HSR is associated with ethnicity among patients exposed to abacavir, and retrospective and prospective studies show a significantly increased risk of abacavir-induced HSR in human leukocyte antigen (HLA)-B*57:01-carrying patients. Immunological studies indicated that abacavir interacts specifically with HLA-B*57:01 and changed the binding specificity between the HLA molecule and the HLA-presented endogenous peptide repertoire, leading to a systemic autoimmune reaction. HLA-B*57:01 screening, combined with patch testing, had clinically predictive value and cost-effective impact in reducing the incidence of abacavir-induced HSR regardless of the HLA-B*57:01 prevalence in the population. Therefore, the US Food and Drug Administration (FDA) and international HIV treatment guidelines recommend a routine HLA-B*57:01 screening prior to abacavir treatment to decrease false positive diagnosis and prevent abacavir-induced HSR. The studies of abacavir-induced HSR and the implementation of the HLA-B*57:01 screening in the clinic represent a successful example of the use of pharmacogenetics for personalized diagnosis and therapy.

personalized medicine, pharmacogenetics, drug safety, abacavir, hypersensitivity reaction (HSR), HLA-B*57:01, HLA-B*57:01 screening

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Abacavir is a nucleoside analog reverse transcriptase inhibitor that is used in combination with other antiretroviral agents to treat human immunodeficiency virus (HIV) infected patients and acquired immunodeficiency syndrome (AIDS) patients [1−3]. Abacavir-induced hypersensitivity reaction (HSR) is the main side effect of the drug, which can be severe, and in rare cases, fatal [4]. Symptoms of abacavir-induced HSR include fever, skin rash, fatigue, gastrointestinal symptoms, and respiratory symptoms. The clinical diagnostic criteria for abacavir-induced HSR require at least two symptoms of fever, rash, nausea, vomiting, headache, lethargy, myalgia, arthralgia or gastrointestinal symptoms, occurring within 6 weeks after commencement, and resolving within 72 hours after withdrawal, of the drug [3,4].

1 Abacavir-induced HSR incidence

Over the last decade, many studies have aimed to determine

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the risk factors of abacavir-induced HSR, and to develop diagnostic methods to identify patients with true abacavir-induced HSR [5]. Epidemiologic analyses of clinical trial data revealed that abacavir-induced HSR occurs in 2.3%–9% of patients exposed to abacavir with incidence differing by ethnicity [6–8]. A meta-analysis conducted by GlaxoSmithKline (GSK), consisting of 5332 patients exposed to abacavir for at least 24 weeks, showed 197 (3.7%) cases of abacavir-induced HSR [9]. In univariate models, differences of incidence rate were found within the expected range of 3%–6%, with the lowest risk of abacavir-induced HSR among African-Americans (3% abacavir-induced HSR) in comparison to other ethnic groups [9]. Later, to more accurately diagnose, report and manage abacavir-induced HSR cases, GSK improved the standardized abacavir-induced HSR case report form for all new protocols to include more comprehensive information for the syndrome, especially the cases with respiratory symptoms. In addition, educational materials and the product label were updated to increase the awareness of the syndrome among patients and healthcare providers. After all these changes, an updated retrospective analysis consisting of 8038 exposure patients was conducted. The new reporting rate for abacavir-induced HSR was dramatically changed from 3.6% to 7.6% (p<0.001), resulting in a change of true incidence rate from 3.7% to 5.0% for abacavir-induced HSR among all patients [10]. These modifications increased the awareness of the syndrome and decreased misclassification of the adverse reaction. Notably, the updated study suggested that African Americans have the lowest risk of developing abacavir-induced HSR after exposure to the drug, in comparison to other ethnicities [9,10].

2 Prevalence and association of HLA-B*57:01 with abacavir-induced HSR

The correlation between ethnicity and the risk of developing abacavir-induced HSR indicated that genetic background might be involved. In 2001, case reports showed that a Caucasian HIV-infected patient and his 9-year-old daughter both developed abacavir-induced HSR after abacavir treatment, suggesting some genetic factors of the symptom [11]. To identify possible genetic markers that are linked to abacavir-induced HSR, 114 polymorphic loci among 12 gene families associated with abacavir metabolism or immune responses were selected to perform association studies [12]. It was found that abacavir-induced HSR was strongly correlated with multiple major histocompatibility complex (MHC) markers. Among them, human leukocyte antigen (HLA)-B57 had a significant association with abacavir-induced HSR with a sensitivity of 46% (39 of 84 patients) and an odds ratio of 23.6 (95% CI 8.0–100, p<0.0001) [12]. Using a high-resolution HLA genotyping method, Mallal et al. [13] more finely mapped the risk allele associated with abacavir-induced HSR to be the HLA-B*57:01, with a sensitivity of 78% (14 of 18 patients with abacavir-induced HSR) and an odds ratio of 117 (95% CI 29–481, p<0.0001). Studies to identify HLA-B*57:01 prevalence in many different ethnic populations have been performed [12–32], and are summarized in Table 1. The highest prevalence (11%) was found in Indian ethnic groups in northern Thailand, while among East Asian populations including Chinese, Korean, and Japanese, HLA-B*57:01 prevalence was relatively low (0–0.3%). The frequency of HLA-B*57:01 in Chinese HIV-infected patients, including North Mainland Chinese, Hong Kong Chinese and Taiwan Chinese, was reported to be 0–2% [22,29,32]. Among 534 Korean and 371 Japanese patients, none had an HLA-B*57:01 allele [19,31]. Caucasians in North America, the UK, Spain, and Australia have a prevalence of the HLA-B*57:01 allele of 6.5%–10% [14,26,30]. African Americans have a prevalence of 1.1%–2.4%, which is higher than the 1% seen in sub-Saharan Africans [23,29]. Surprisingly, no HLA-B*57:01 alleles were found in 247 Ugandan HIV-infected patients [25].

Progress was rapid in identifying and putting into clinical practice the association between HLA-B*57:01 and abacavir-induced HSR. As shown in Table 2, abacavir-induced HSR is consistently associated with HLA-B*57:01. In 2002, Mallal et al. first described the association between HLA-B*57:01 and abacavir-induced HSR in Western Australian patients [13]. The allele frequency of HLAB*57:01 for abacavir-induced HSR patients was 78%, whereas it was 2% in HSR-free subjects. However, in this study only one clinician was taking the responsibility to review patients' records of abacavir treatment history and responses of drug reactions, with limited experience in diagnosis/evaluation/classification of abacavir-induced HSR at the time when the syndrome was just becoming recognized. Therefore, the potential for false diagnosis of abacavir-induced HSR was inevitable. At the same time, another case-control study was reported by Hetherington et al. [12]. This study included 85

Table1 Prevalence of HLA-B*57:01 in different populations

Race/region	Frequency (%, *n*/*n*)	Year (ref.)
Asian		
North Thailand	11 (n/a)	2003 [26]
Chinese	0.3 (1/320)	2007 [32]
Korean	0 (0/534)	2009 [27]
Japanese	0 (0/371)	2000 [31]
Caucasian		
Canada	4.1 (20/489)	2012 [15]
Spain	6.5 (78/1198)	2009 [14]
Australia	7.7 (20/260)	2006 [30]
African Descendant		
African American	1.1–2.4 (n/a)	2003 [26]
Ugandan	0 (0/247)	2011 [25]

Table2 Association of HLA-B*57:01 with abacavir-induced HSR

Caucasian		African Descendant		Other		Year (ref.)
Case (*n*/*n*)	Control (*n*/*n*)	Case (*n*/*n*)	Control (*n*/*n*)	Case (*n*/*n*)	Control (*n*/*n*)	
78% (14/18)	2% (4/167)					2002 [13]
55% (36/65)	1% (1/80)	0% (0/9)	0% (0/18)	10% (1/10)	0% (0/15)	2002 [12]
94% (17/18)	2% (4/230)					2004 [21]
46% (6/13)	10% (5/501)					2004 [18]
44% (57/13)	4% (8/202)	14% (10/69)	<1% (2/206)			2008 [33]
94% (15/16)	1% (2/307)			100% (3/3)	0% (0/163)	2012 [15]

patients with abacavir-induced HSR (cases) and 115 patients who were HSR-free after exposure to abacavir treatment for at least 6 weeks (controls). It was found that the HLA-B*57:01 allele frequency in abacavir-induced HSR patients was much higher than that of HSR-free patients (36/65 vs. 1/80, resulting in a sensitivity of 55%). Compared with the Western Australian study [13], this study showed a lower sensitivity (55% vs. 78%), indicating that the degree of association between the HLA-B* 57:01 allele and abacavir-induced HSR varied across different populations. Martin et al. further explored the association between HLA-B*57:01 and abacavir-induced HSR in a larger Western Australian cohort [21], and found that 94.4% (17/18) of patients who were clinically diagnosed with abacavir-induced HSR carried an HLA-B*57:01 allele while only 1.7% (4 of 230 subjects) of the HSR-free control group carried it. Compared to their previous study [13], an epicutaneous patch test (a well-accepted testing method for diagnosis of allergic contact dermatitis) was employed in the recent study [21] to make the HSR diagnosis more accurate. This significantly increased the HLA-B*57:01 sensitivity of detection of abacavir-induced HSR from 78% to 94% in the same ethnicity [13,21]. The advantage of the patch test will be further discussed below.

In a more comprehensive study, Hughes et al. [17] performed genetic association studies among Caucasians, African Descendants and Hispanics, and results showed that HLA-B*57:01 was strongly associated with abacavir-induced HSR in Caucasians with a sensitivity of 40%–52% (p=4.7×10^{-18} in males), depending on the study and analysis population. The association was moderate in Hispanics with a reduced sensitivity of 20%–22% (p=2.1×10^{-4}). In the African Descendant population, however, the association was not statistically significant (p=0.27). The lower sensitivity in this study might be due to the reasons that more diverse population was recruited and patch test was not applied. The insignificant association between HLA-B*57:01 and abacavir-induced HSR in African Descendants might be due to the relatively small sample size (37 cases and 41 controls) in this study. A similar sensitivity was reported among Caucasians from the UK [18]. Most recently, the strongest association between HLA-B*57:01 and abacavir-induced HSR was reported from a southern Alberta based population, in which cases are dominantly Caucasians but without detailed stratification with other ethnicities with an odds ratio of 6934 (95% CI 321–149735) and a sensitivity of 90% (18 of 20 patients with abacavir-induced HSR) [15]. Saag et al. [33] used the patch test for immunological confirmation of abacavir-induced HSR and showed 100% sensitivity of HLA-B*57:01 as a marker for abacavir-induced HSR in both Caucasian and African Descendant populations. Thus, there is strong evidence for the risk allele HLA-B*57:01 being a reliable predictor of abacavir-induced HSR in Caucasian patients. In non-Caucasian patients, the reliability of this marker is not as robust. This may be because of the relatively small samples sizes, and is complicated by the relatively low prevalence of the HLA-B*57:01 allele in many non-Caucasian ethnic groups (Table 1). The more objective measurement of HSR by utilization of the patch test appears to improve the reliability of the genetic association studies, and suggests that prospective screening for the HLA-B*57:01 allele in HIV patients should reduce the incidence of abacavir-induced HSR [3].

3 Underlying mechanisms of the association between HLA-B*57:01 and abacavir-induced HSR

In general, the lack of full understanding of the complex interactions among HLA-molecules, antigens, and T-cells hinders the understanding of the underlying mechanisms of drug-induced hypersensitivities. However, several mechanistic models have been postulated to explain the adverse reaction. First, the hapten (or prohapten) theory proposes that small molecules (haptens) can bind to a peptide or protein, thus changing the immunogenicity of the complex. The hapten model tries to explain the adverse drug reaction as a consequence of the drug (or drug metabolites) binding to proteins or peptides, and then the "modified" protein or peptide becomes a new antigenic determinant that elicits an immune response [34,35]. The second model is the pharmacological interaction with immune receptors (p-i) model, postulating that drugs can directly or reversibly bind to T-cell receptors and/or the HLA-peptide complex, triggering the T-cell mediated immune reactions [36,37]. The third model, referred to as the danger model, hypothesizes that the major determinant of an immune response by some

drugs is whether the drugs cause particular types of cell damage. If the drugs cause these types of cell damage, they induce immune hypersensitivity reactions [38,39]. Each of these models can explain some aspects of the phenomena observed in adverse drug reactions; however, complete understanding remains incomplete, especially for the detailed mechanism of the molecular interactions between drugs and the immune system.

The first evidence provided by wet-lab experiments showed that the activation of $CD8^+$ cells to produce cytokines was driven by abacavir-HLA-B*57:01 specific binding [40]. In this study, it was demonstrated that (i) the interaction between HLA molecule and the drug is restricted by both the specificity of the HLA-B*57:01 and the uniqueness of ligand-abacavir; (ii) abacavir-induced responses require the activation of conventional HLA-antigen-presentation pathway; and (iii) the distinct architecture of the F-pocket (one of the peptide binding pockets for antigen presenting) of the HLA molecule specifies the antigen binding affinity.

On the other hand, based on prior knowledge in protein-drug interaction and data mining, an *in silico* approach was proposed by Yang et al. [41] to explain the underlying mechanisms of adverse drug reactions through specific protein-drug interactions. By analyzing the binding strength and binding conformation changes among 162 drug molecules and 845 proteins, they predicted the specific binding interaction between abacavir and HLA-B*57:01 molecule (not HLA-B*57:03) mediates skin hypersensitivity. Most recently, the mechanism has been further revealed that abacavir selectively interacts with HLA-B*57:01 inducing a conformational change which leads to altered binding between the HLA molecule and the HLA presented endogenous peptide repertoire. Briefly, abacavir binds to the bottom of the antigen-binding cleft in HLA-B*57:01, which changes the shape and chemistry of the cleft and leads to alterations in the ability to bind the normal repertoire of endogenous peptides. Thus, new self-immunological peptides can activate and drive T-cells response, leading to cytokine production that induces an idiosyncratic adverse drug reaction [42,43].

4 Role and benefit of HLA-B*57:01 screening

The results from association and mechanism studies on the interaction between HLA-B*57:01 and abacavir-associated HSR imply that HLA-B*57:01 screening has predictive value for patients prior to abacavir treatment. To evaluate the clinical utility of HLA-B*57:01 screening, a prospective study was performed in 260 Western Australia patients [30]. This study showed that the incidence of abacavir-induced HSR was 2%, and none of the 148 HLA-B*57:01-negative patients developed abacavir-related HSR, indicating the benefit of HLA-B*57:01 screening for reducing the incidence of HSR [30]. These results were confirmed in the UK and France, where the incidence of abacavir-induced HSR decreased from 12% to less than 0.5% following introduction of HLA-B*57:01 screening [44,45]. Therefore, prospective HLA-B*57:01 screening has shown predictive benefits for HLA-B*57:01 carrying patients in avoiding abacavir-induced HSR.

Furthermore, studies suggested HLA-B*57:01 screening was cost-effective, especially for populations with high HLA-B*57:01 prevalence [18,20,46–48]. A double-blind trial was designed to evaluate the clinical usefulness of HLA-B*57:01 screening in Europe and Australia, and included 1956 HIV-infected patients [20]. In the study, patients were randomly divided into two groups: one group was assigned to have the routine HLA-B*57:01 screening prior to abacavir treatment and only HLA-B*57:01 negative patients received abacavir therapy (screening group); the other group was assigned to receive abacavir treatment without HLA-B*57:01 screening (control group). Patch testing was applied in the study to confirm a true HSR diagnosis. In the control group, the incidence of abacavir-induced HSR was 2.7%; in contrast, no abacavir-induced HSR cases were found in the screening group. Combined with patch testing, HLA-B*57:01 screening showed an advantage in reducing the incidence of HLA-B*57:01-induced HSR, implying its clinical value. Studies in Spain and Canada also confirmed the predictive value of HLA-B*57:01 screening for HIV-infected patients in preventing HSR development [49,50].

The cost of abacavir treatment (in combination with other drugs) is approximately 1500–3300 USD per month [15,48] and HLA-B*57:01 genotype screening in western countries adds a relatively small cost (100 USD) [15,45,48]. However, the cost of diagnosis and treatment of a severe HSR ranges from 3500 to 30000 USD, depending on the severity level [48]. Thus, compared with the cost incurred for treating an abacavir-induced HSR, the small incremental cost of genotypic screening for the HLA-B*57:01 allele prior to abacavir treatment is dramatically cost-effective

Prior studies showed that African Descendant and some Asian populations have a relatively low frequency of the HLA-B*57:01 allele [10,26,27]. In those populations, HLA-B*57:01 screening is still useful to decrease false positive diagnosis of abacavir-induced HSR by combination with patch testing. The patch testing was first applied by GSK researchers in the study of abacavir-induced HSR [3], and has been widely adopted to identify abacavir-induced HSR. Several studies have shown that patch testing significantly reduced false diagnosis of abacavir-induced HSR [21,47,51,52] and strengthened the genotype-phenotype association. By combining with patch testing, HLAB*57:01 screening had 100% sensitivity to predict abacavir-induced HSR regardless of race, indicating that such screening could be valuable to prevent abacavir-induced HSR even in populations with low prevalence of HLA-B*57:01 [31,53]. Cur-

rently, HLA-B*57:01 screening is available in most western countries, and international HIV treatment guidelines recommend routine HLA-B*57:01 screening prior to abacavir treatments [4,45]

5 Summary and perspectives

Abacavir is an effective anti-retroviral drug for HIV-infected patients. The major clinical limitation of abacavir is its adverse reaction—hypersensitivity syndrome. Both retrospective and prospective studies showed strong association between the HLA-B*57:01 allele and abacavir-induced HSR. Mechanistic studies support a novel autoimmunity model, in which abacavir alters the self-peptide binding to HLA-B*57:01 and leads to autoimmune reactions. As summarized in Figure 1, HLA-B*57:01 is a risky allele for the development of abacavir-induced HSR. Prospective HLA-B*57:01 screening has been shown to prevent abacavir-induced HSR in HIV-infected patients. Accordingly, the FDA approved an important safety-related label update for abacavir in 2008 that recommends patients be screened for the HLA-B*57:01 allele prior to initiating abacavir-containing treatment. HLA-B*57:01 screening represents a successful example of the application of pharmacogenetics approaches to the realization of personalized medicine.

Some questions remain, however. For example, why don't all patients with the HLA-B*59:01 allele get abacavir-induced HSR? The incidence of abacavir-induced HSR is approximately 60% in HLA-B*57:01 carriers, so what are the other risk-modifying factors? Does any other variability play a role in the development of the drug adverse reaction? Given the fact that many biological components, such as T-cell receptors and drug metabolizing enzymes, are also involved in the hypersensitivity reactions, other genetic markers (as well as non-genetic factors) may be associated with abacavir-induced HSR. Together with the HLA-B*57:01 allele, such biomarkers will provide better predictive information for the safe use of this drug. Next-generation sequencing (NGS) is fundamentally changing the way in which genomic information of individuals at the DNA and RNA level is being studied, and enables a better understanding of human genetics to empower personalized medicine [54,55]. The revolutionary power of NGS enables higher sensitivity in detecting genetic variants with more specificity and capability, providing enormous opportunities and potential for researchers working in medicine, biology and life sciences. Along with the development of robust informatics tools for nucleotide variant detection, *in silico* molecular modeling approaches should help us better understand and predict interactions between specific drugs and HLA variant proteins. Thus, the combined approaches of genetic association studies, wet-lab mechanistic experiments, and molecular modeling promise to answer these questions and lead to the reduction of drug-induced adverse reactions.

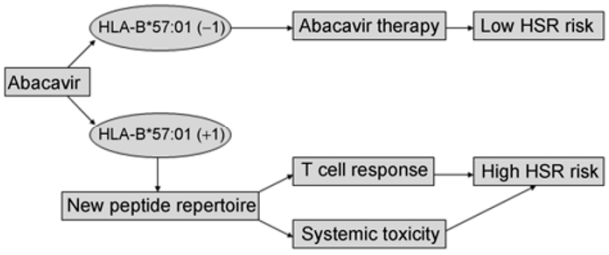

Figure 1 HLA-B*57:01 is a risky allele for the development of abacavir-induced HSR.

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