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Pharmacogenetics of drug hypersensitivity

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Abstract

Drug hypersensitivity reactions and severe cutaneous adverse drug reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, are examples of serious adverse drug reactions mediated through a combination of metabolic and immunological mechanisms that could traditionally not have been predicted based on the pharmacological characteristics of the drug alone. The discovery of new associations between these syndromes and specific HLA has created the promise that risk for these reactions could be predicted through pharmacogenetic screening, thereby avoiding serious morbidity and mortality associated with these types of drug reactions. Despite this, several hurdles exist in the translation of these associations into pharmacogenetic tests that could be routinely used in the clinical setting. *HLA-B*5701* screening to prevent abacavir hypersensitivity syndrome is an example of a test now in widespread routine clinical use in the developed world.

Keywords

HIV; human leukocyte antigen; hypersensitivity; pharmacogenetics; pharmacogenomics; Stevens–Johnson syndrome; toxic epidermal necrolysis

Drug hypersensitivity & related syndromes

Although adverse drug reactions comprise a significant burden of morbidity and mortality in the community, approximately 80% of adverse drug reactions are predictable and hence preventable based on their pharmacological mode of action. From a clinical standpoint, adverse drug reactions have been classified into type A (predictable based on pharmacological action of the drug) and type B (not predictable based on the pharmacological action of the drug, less dependent on dose and largely driven by host genetics) [1,2]. In view of the fact that type B reactions are less common and historically not predictable or preventable, they have been a common cause for the withdrawal of drugs in both the premarketing and postmarketing phase of drug development. Many type B reactions are thought to be immunologically mediated. The Gell and Coombs classification divides immuno logically mediated drug reactions into four categories, I–IV, based on their presumed immunopathogenesis. A more simplistic

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categorization classifies these drug reactions into immediate reactions, which are IgE-mediated reactions that typically occur within hours of exposure to the drug, and delayed hypersensitivity reactions that typically occur more than 72 h after exposure to the drug. Since there have been few defined pharmacogenetic associations with immediate hypersensitivity reactions, the focus of this article will be on the pharmacogenetics of delayed drug hypersensitivity reactions, which include hypersensitivity syndromes (drug-induced hypersensitivity syndrome [DIHS] and drug reaction with eosinophilia and systemic symptoms [DRESS]) and single-organ drug-induced diseases, such as drug-induced liver disease (DILI), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Notably, DILI in association with some drugs may be nonimmunologically mediated. Although many drugs have been described in association with these types of immunologically mediated reactions, the most commonly implicated drugs across diverse populations include antiretrovirals, allopurinol, anticonvulsants, β-lactam antimicrobials, nonsteroidal anti-inflammatory agents and sulfa antimicrobials, and other aromatic sulfonamides.

A major and recent advance in the field of adverse drug reactions has been the elucidation of associations between HLA alleles and drug hypersensitivity and related syndromes associated with specific drugs (Table 1) [3–40]. This has added to the evidence base that these reactions are immunologically mediated and has furthered the understanding of their immunopathogenesis. Furthermore, these HLA associations offer promise that type B drug reactions that are unpredictable based on the pharmacological action of the drug could be both predictable and preventable in the future. Although many early studies used candidate gene approaches, more recent genome-wide association studies have the advantage of identifying multiple targets and potentially adding to the positive predictive value. In the case of genome-wide and HLA association studies, confirmatory haplotype-mapping studies are required to more definitively identify the susceptibility region responsible.

More severe manifestations of delayed drug hypersensitivity have included a combination of fever, varying severity of rash and internal organ involvement, typically occurring in the second week or later after initiation of treatment. The most common internal organ manifestation is hepatitis; however, pancreatitis, interstitial lung disease, nephritis, myositis or myocarditis are other less common manifestations. Hematological manifestations, including atypical lymphocytosis and eosinophilia, are common, and in conjunction with the other manifestations may lead to confusion with viral illness (atypical lymphocytosis) and other infectious diseases. In an attempt to add consistency to the nomenclature of delayed drug hypersensitivity with systemic symptoms, different acronyms that refer to the same syndrome have been developed with no real preferred consensus of which term to use as yet. These include DIHS and DRESS. These terms have been devised to describe more specific syndromes often occurring greater than 3 weeks after drug initiation, and a minimum criteria set of fever, rash, hepatitis and white cell abnormalities for DIHS has been proposed [41–43]. More recently, drug-induced skin injury has been proposed as a overarching term to reflect all drug-induced skin disease. Reactivation of chronic persistent human herpes viruses, such as human herpesvirus 6 and cytomegalovirus, have also been described during the course of DIHS/DRESS, and have been associated with recurrence of symptoms 2–3 weeks or later after the drug has been discontinued [42,44–46]. Long-term sequelae described in conjunction with DIHS/DRESS have included autoimmune phenomena, such as thyroiditis and systemic lupus erythematosis [47,48].

Common drugs associated with DIHS/DRESS and related drug hypersensitivity syndromes include the aromatic amine anticonvulsants (carbamazepine, phenytoin and pheno-barbital), lamotrigine, allopurinol, NSAIDs, sulfa antimicrobials and aromatic sulfamonamides, and antiretroviral agents (abacavir, nevirapine and fosamprenavir).

Unifying hypotheses have been proposed as the basis for these syndromes. The danger hypothesis suggests that a stressor or signal, in the form of infection, surgery or any other proinflammatory process, is necessary to promote the antigenic response [49]. The hapten hypothesis applies to small-molecule drugs where the immune response requires modification of a host protein or peptide by a reactive metabolite of the drug in question [50]. The pharmacological interaction theory, which has been proposed by Pichler, suggests that under specific circumstances some drugs may activate T cells by directly interacting with the MHC-peptide and/or T-cell receptor [51]. Although these hypotheses have been constructed to apply to DIHS/DRESS, drugs may be associated with single organ disease without the presence of rash or fever, such as DILI associated with flucloxacillin or amoxicillin–clavulanate or single-organ disease associated with tetracycline antimicrobials [52]. Similar to DIHS/DRESS, a combination of metabolic, immunologic and genetic factors are also thought to contribute to the pathogenesis of many drug-induced single-organ diseases, although, as previously mentioned, for some drugs, DILI may be mediated by nonimmunologic mechanisms.

Drug-induced reactions that are clinically and pathophysiologically distinct from DIHS/DRESS and other drug hypersensitivity reactions include SJS and TEN. Although SJS/TEN share some clinical and laboratory features with DIHS/DRESS, particularly in terms of their delayed onset, association with fever and internal organ involvement and in some instances human herpesvirus 6 reactivation, they differ in that they are characterized by blistering skin disease with mucosal and often ocular involvement [53]. Like DIHS/DRESS, the onset of symptoms of SJS/TEN is commonly within the first 1–3 weeks following first exposure, with most patients presenting within 8 weeks. SJS and TEN are a spectrum of disease defined according to the presence of skin separation and percentage of body surface area involved. SJS occurs when less than 10% body surface area is involved, TEN when more than 30% total body surface area is involved, and SJS–TEN overlap when 10–30% body surface area is involved [54,55]. Although SJS/TEN are uncommon, the morbidity and mortality are high, ranging from 1–5% mortality for SJS to 30–50% for TEN. Drugs causing SJS/TEN overlap considerably with those causing DIHS/DRESS, with the most common being allopurinol, aromatic amine anticonvulsants, antiretrovirals (most commonly nevirapine), NSAIDs and sulfa antimicrobials. Although abacavir has been commonly associated with a drug hypersensitivity syndrome, there have been only two published case reports of SJS/TEN potentially associated with abacavir in the English literature despite over 10 years of postmarketing experience [56, 57]. In one case of SJS, the patient had advanced HIV and infectious comorbidities [56], and in the other case, TEN occurred in a patient with advanced HIV 4 months after starting treatment with abacavir, lamivudine and darunavir/ritonavir [57]. Hence, abacavir is not listed as a drug usually associated with this syndrome. The clinical manifestations of TEN are thought to be the result of massive and widespread death of keratinocytes and mucosal cells. Although previous syudies suggested that this process was triggered by Fas, Fas ligand and granzyme B, more recent studies suggest that secretory granulysin mediated the generalized keratinocyte apoptosis [58–61]. Moreover, quantities of granulysin in blister fluid appear to correlate with the severity of SJS/TEN [58]. It is likely that SJS/TEN is mediated by a $CD8^+$ T-cell class I HLA-restricted process, which has been more recently supported by studies associating HLA Class I alleles with drug-associated SJS/TEN (Table 1) [61]. Early recognition of SJS/TEN is important, as the mainstay of management is aggressive supportive care, as the main morbidity and mortality is from infectious complications.

Specific drug syndromes & pharmacogenetics

Drug hypersensitivity has been described in association with many drugs; however, for most of these, a specific pharmacogenetic association has not been defined. For others, specific HLA associations have been described, but these do not seem to be generalizable across different populations or ethnicities [62]. For many drugs, associations between drug hypersensitivity

and related syndromes and a single gene or HLA allele may not exist, or may not be generalizable across different populations and races (Table 1) [3–40]. Another potential explanation for this may be that some drugs are metabolized to a reactive metabolite by genetically polymorphic enzymes that differ in prevalence across race and population. An additional challenge is the rather nonspecific phenotype of some of these drug-induced syndromes, which may be confused with infection or other inflammatory disease [63]. Drug-induced syndromes, such as isolated delayed skin rash without fever or internal organ involvement, DIHS/DRESS and SJS/TEN, need to be treated as phenotypically distinct entities, as they are also pathophysiologically distinct, rather than being a spectrum of the same disease. Each entity is therefore likely to have a different pharmacogenetic basis. Unfortunately, diagnostic tests either to improve the specificity of each of these phenotypes or to confirm the diagnosis do not exist for most drugs.

Abacavir

Abacavir is a guanosine analog that works by competitively inhibiting the reverse transcriptase of HIV, and is used effectively in combination with other antiretroviral drugs. Abacavir, which has been approved for use since 1998 in most developed countries, has been associated with a diagnosis of hypersensitivity syndrome in approximately 8% of patients who start the drug [64]. Symptoms of abacavir hypersensitivity (ABC HSR) differ from other drugs associated with DIHS, occurring at a median value of 9 days after first initiation of the drug [64]. Symptoms and findings are nonspecific and include fever, malaise, gastrointestinal symptoms and internal organ involvement. Rash tends to be mild to moderate, occurring in 70% of patients with ABC HSR and often late in the course of disease. Unlike DIHS/DRESS associated with other drugs, eosinophilia and hepatitis are uncommon. The hallmark of the syndrome is that symptoms will completely disappear within 72 h of discontinuation; however, re-exposure can result in severe hypotension and even death [65].

The first suggestion of a potential genetic association with ABC HSR came with postmarketing experience that showed lower frequency of ABC HSR in black and Asian populations [66], as well as a case report of ABC HSR occurring in a father and daughter [67]. In 2002, two independent groups reported an association between *HLA-B*5701* and ABC HSR [10,11]. Hurdles to the immediate application of *HLA-B*5701* as a screening test to prevent ABC HSR included concerns regarding the less than 100% negative predictive value of the test in early studies and the apparent low sensitivity of *HLA-B*5701* for ABC HSR in nonwhite populations (Figure 1). These initial hurdles were driven by the high rate of false-positive clinical diagnosis of ABC HSR, which was actually a necessary clinical strategy in the early postmarketing years of the drug in order to prevent the morbidity and mortality associated with ABC HSR [68]. The high rate of false-positive clinical diagnosis was particularly apparent in those of nonwhite race who have a low carriage rate of *HLA-B*5701* and where false-positive ABC HSR diagnosis overshadows true-positive ABC HSR [68]. The problem with false-positive clinical diagnosis is highlighted in abacavir randomized double-blind clinical trials, where between 2 and 7% of patients not receiving abacavir consistently received a clinical diagnosis of ABC HSR [69–72]. Abacavir skin patch testing proved to be a highly specific test for the identification of true immunologically mediated ABC HSR, and a means of overcoming the problem of false-positive clinical diagnosis (Figure 1) [73–75]. Correlation between skin biopsies from the rash from acute ABC HSR and from a positive abacavir patch test, both showing an abundance of $CD4^+$ and $CD8^+$ cells, are consistent with the hypothesis that patch testing involves reproduction of a local hypersensitivity reaction in the skin [73].

More recently, two studies that have incorporated skin patch testing into their study design that have provided high-level evidence to support the clinical effectiveness of *HLA-B*5701* screening to prevent ABC HSR. The Prospective Randomized Evaluation of DNA Screening

in a Clinical Trial (PREDICT-1) study was a randomized, double-blind, controlled study that randomized patients either to receive real-time *HLA-B*5701* screening and exclusion of abacavir in those positive for *HLA-B*5701* or abacavir initiation and clinical monitoring with retrospective *HLA-B*5701* analysis [76]. The study enrolled 1956 patients, of whom 84% were Caucasian, and demonstrated that *HLA-B*5701* screening eliminates patch-test-positive (immunologically confirmed) ABC HSR. This 100% negative predictive value supports the broad clinical utility of *HLA-B*5701* as a screening test for the prevention of ABC HSR [76]. The Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) study was a case–control design that enrolled both white and black patients in the USA to examine the generalizability of the sensitivity and specificity of *HLA-B*5701* for patch-test-positive ABC HSR across ethnicity [77]. This study showed that 100% of both white and black patch-test-positive patients carried *HLA-B*5701*, suggesting a 100% negative predictive value of *HLA-B*5701* for ABC HSR, generalizable across race [77].

Further clinical evidence was generated through observational studies that have effectively shown that open screening not only eliminates true immunologically mediated ABC HSR, but also significantly decreases false-positive clinical diagnosis [78–84].

Concurrent with evidence to support the clinical effectiveness of *HLA-B*5701* as a screening test to predict and prevent ABC HSR, a body of science evolved in parallel that supports the necessity of *HLA-B*5701* for the development of ABC HSR [85–87]. Conclusive experimental work has demonstrated that ABC HSR is *HLA-B*5701* restricted and mediated by $CD8^+$ T lymphocytes. Further evidence supports the notion that $CD8^+$ T-cell responses can be demonstrated from peripheral blood mononuclear cells from *HLA-B*5701*-positive, abacavir-naive healthy blood donors that have undergone 12-day culture and restimulation with abacavir-pulsed *HLA-B*5701* transfected antigen-presenting cells [85]. A single amino acid change within the peptide-binding domain, such as the substitution of a serine to a tyrosine at position 116 of *HLA-B*5701*, will completely abrogate recognition by abacavir-specific $CD8^+$T cells, which again strongly supports the point that abacavir hypersensitivity is mediated exclusively through *HLA-B*5701* [85]. Although all current evidence supports that *HLA-B*5701* is necessary for the development of ABC HSR, it is not sufficient. The PREDICT-1 study suggested that *HLA-B*5701* has a positive predictive value of 55%. Further studies have explored other candidate genes in an attempt to explain why 45% of patients who carry *HLA-B*5701* do not develop ABC HSR. To date, there have been no definitive clues, although it seems likely that the pathway to *HLA-B*5701*-positive abacavir tolerance may be diverse and outside of the MHC [88].

Nevirapine

Nevirapine is another antiretroviral agent used in combination therapy for the treatment of HIV that belongs to the non-nucleoside reverse transcriptase inhibitor class. Nevirapine has been commonly associated with isolated delayed skin rash, which is the most common treatment-limiting toxicity. DIHS/DRESS occurs in approximately 5% of those starting nevirapine and is typically associated with fever, rash and hepatitis [89,90]. Isolated hepatitis and SJS/TEN also occur typically 2–6 weeks after initiating nevirapine.

Different Class I and Class II HLA associations have been described in association with nevirapine rash and DIHS/DRESS across different populations [12–15]. This suggests that there may be more than one immunologic and genetic pathway leading to the development of nevirapine rash and DIHS/DRESS, which could be related to genetic differences in drug metabolism (e.g., cytochrome P450 2B6) in different populations. These reactive metabolites, which may be distinct across populations, may then trigger class I-restricted $CD8^+$-mediated or class II-restricted $CD4^+$-mediated immune responses in the presence of the relevant respective Class I and II MHC alleles. The first reported nevirapine HLA study was a

population-based study from Western Australia that showed an association with the MHC Class II allele *HLA-DRB1*0101* and rash-associated hepatitis [12]. This effect occurred in patients with a $CD4^+$ percentage of over 25, suggesting that CD4 depletion has an effect on abrogating nevirapine DIHS/DRESS and, in keeping with previously published clinical data, suggesting a higher rate of nevirapine reactions in women with $CD4^+$ over 250/μl and men with $CD4^+$ over 400/μl, and severe reactions occurring in HIV-uninfected individuals treated with nevirapine for postexposure prophylaxis. Animal and cellular models have also supported that nevirapine DIHS/DRESS is a $CD4^+$-dependent process [90]. Another study that resolved HLA to two (low-resolution) rather than four (high-resolution) digits suggested an association between *HLA-DRB1*01* and rash with both nevirapine and another non-nucleoside reverse transcriptase inhibitor, efavirenz [20]. Several other studies have associated nevirapine DIHS/DRESS with Class I HLA alleles, including *HLA-B*1402* and *HLA-Cw8* in a Sardinian population [13] and *HLA-Cw8* in a Japanese population [14]. A recent case–control Thai study associated nevirapine rash and DIHS/DRESS with *HLA-B*3505*, which occurred in 17.5% of HIV patients with nevirapine rash or DIHS/DRESS versus 1.1% of nevirapine controls and under 1% of the Thai population [15]. In a more recently published Thai case–control study from a different group, HLA-Cw4 was over-represented in the group with nevirapine-associated rash [91]. This apparent association with HLA-Cw4, however, most likely reflects the fact that it is in linkage disequilibrium with *HLA-B*3505*, as the corrected p-value for HLA-Cw4 did not reach significance in the first Thai study [15], and the authors had not carried out HLA-B typing in the second study [91].

Occurrence of SJS/TEN in patients initiating nevirapine is currently 0.3% or less. To date, no specific genetic or HLA association has been described in associated with nevirapine SJS/TEN. However, genetic factors are suggested in a report of nevirapine-associated SJS occurring in a mother and son [92].

Aromatic amine anticonvulsants

The aromatic amine anticonvulsants, carbamazepine, phenobarbital and phenytoin, are associated with a DIHS/DRESS that usually occurs 2–8 weeks following drug initiation [93]. Clinically, the reactions are marked by fever, rash, internal organ involvement and lymphadenopathy. Aromatic amine anticonvulsants are metabolized to arene oxide metabolites. It is thought that the pathophysiology of this syndrome may be mediated through both immunologically-mediated and nonimmmulogically mediated mechanisms, such as direct cellular toxicity of the arene oxide metabolites [93]. Clinical cross-reactivity between the aromatic amine anticonvulsants is thought to occur in approximately 70–80% of those who have experienced a reaction with one aromatic amine anticonvulsant [94]. To date, there have been no generalizable pharmacogenetic associations that have been elucidated for aromatic amine anticonvulsant DIHS/DRESS. A study in a Han Chinese population suggested that isolated rash associated with carbamazepine may be associated with *HLA-A*3101*, and DIHS/DRESS with SNPs in the motilin gene (rs2894342) [16]. Previous studies in Caucasians that have included mixtures of patients with DIHS/DRESS and SJS/TEN have associated alleles on the ancestral 8.1 haplotype, and suggest that *HLA-B*0702* may be protective against the development of carbamazepine DIHS/DRESS [17,18]. Another study suggested an association between carbamazepine DIHS/DRESS and polymorphisms in a central MHC region, which includes three HSP70 genes, although it is also possible that the effect is mediated by specific Class I or II HLA alleles in linkage disequilibrium with these central HSP70 haplotypes [95]. To date, neither SNPs in genes associated with carbamazepine metabolism nor activity of lymphocyte microsomal epoxide hydrolase have been associated with carbamazepine DIHS/DRESS/SJS/TEN [16,96].

The most serious type B adverse drug reactions occurring in association with aromatic amine anticonvulsants are SJS/TEN. These reactions are rare in European populations, occurring in 1–6 out of 10,000 individuals initiating therapy with these anticonvulsants. In a Han Chinese and other Southeast Asian populations it is estimated that these reactions occur greater than tenfold more commonly. In 2004, a case–control study reported a strong association between *HLA-B*1502* and SJS/TEN in a Han Chinese population and suggested a 100% negative predictive value of *HLA-B*1502* for carbamazepine-associated SJS/TEN [5]. In this study, 100% of 44 Han Chinese patients were *HLA-B*1502* positive versus 3% of 101 tolerant patients and 9% in the general population [5]. *HLA-B*1502* is in fact a marker for Chinese and Southeast Asian ancestry, and a carriage rate of 10–15% is also in keeping with the significantly higher prevalence of SJS/TEN associated with aromatic amine anticonvulsants in these areas. In addition, further studies have replicated the association between *HLA-B*1502* and carbamazepine-associated SJS/TEN in Chinese and Thai populations [6,7,16] but not in Japanese and Caucasian populations, where the prevalence of *HLA-B*1502* is less than 0.1% [8,97–99]. Based on this information, and further to a review by the US FDA, the carbamazepine product label changed to warn against the use of carbamazepine in Asian patients or those of known *HLA-B*1502* status. However, concerns arise regarding the accuracy of self-identified or physician-assigned ethnicity. In addition, a recent Thai study has also associated *HLA-B*1502* with phenytoin-asociated SJS [7].

Although there is limited information on HLA cross-reactivity between the aromatic amine anticonvulsants, given the emergence of some data to support an association between *HLA-B*1502* and phenytoin SJS/TEN, and the known clinical cross-reactivity between these drugs, a cautious approach would be to avoid the future use of all aromatic amine anticonvulsants when a patient has had a serious reaction associated with one member of this group.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor used to prevent the common disorders gout and hyperuricemia. A case–control study in a Han Chinese population published in 2005 showed a strong association between the HLA class I allele, *HLA-B*5801* and allopurinol-associated DIHS/DRESS and SJS/TEN [3]. In this study, all 51 out of 51 patients (100%) with allopurinol SJS/TEN or DIHS/DRESS carried *HLA-B*5801* versus 20 out of 135 (15%) of allopurinol-tolerant patients and 19 out of 93 (20%) population controls ($p < 0.00001$; odds ratio: 580) [3]. A second case–control study in a Thai population showing a similarly strong association between *HLA-B*5801* and allopurinol SJS/TEN supports the idea that this association may be generalizable across other Southeast Asian populations [4]. *HLA-B*5801* as an allele is more broadly distributed than *HLA-B*1502*, with the allele carriage rate being 1–6% in Caucasians, 2–4% in Africans and less than 0.4% in Japanese. Although there is less information regarding the association between allopurinol SJS/TEN or DIHS/DRESS in these other populations, a recent study demonstrated that 55% of European ancestry Caucasians with allopurinol-associated SJS/TEN carried *HLA-B*5801*, and a smaller Japanese study reported that four patients with allopurinol-associated SJS/TEN and *HLA-B*5801* [8,97].

Future challenges: translating pharmacogenetic research into clinical practice

New and high-throughput technologies have driven medical research into a pharmacogenomic era with an enormous flood of data and publications. When it comes to the prospect of using pharmacogenetic testing to guide the treatment of the individual patient in everyday clinical practice, the current challenges are enormous. For drug hypersensitivity reactions and related adverse drug reactions that are sometimes referred to as idiosyncratic, pharmacogenetics

provides enormous opportunities not only to shed light on the pathophysiology of these reactions but also to be able to predict and prevent their occurrence.

The example of the antiretroviral drug abacavir has created a translational roadmap and has reality tested the considerable number of steps and hurdles involved in taking a pharmacogenetic test from discovery to a test used in real clinical practice (Table 2) in most of the developed world, which has been endorsed by international HIV treatment guidelines [100,101,201]. A number of issues were unique with regards to abacavir, however, that may not apply as easily to other drugs (Table 2) [102]. This includes the fact that although true immunologically mediated abacavir hypersensitivity occurs in 3–4% of Caucasian populations, it is diagnosed in 6–12% because of the high false-positive clinical diagnosis rate. Therefore, the implications are that *HLA-B*5701* screening prevents not only true immunologically mediated abacavir hypersensitivity but also false-positive clinical diagnosis (Figure 1). Moreover, *HLA-B*5701* screening prior to abacavir exposure protects a population at risk from exposure to abacavir, and this not only prevents the development of a primary immunologic response that would lead to ABC HSR, but is also an additional safeguard against the severe morbidity and even mortality that can occur on inadvertent rechallenge to abacavir.

The accuracy and specificity of the clinical phenotype of drug hypersensitivity and related reactions is extremely important and can be a major limiting factor in attempting to determine pharmacogenetic associations, whether taking a candidate or a whole-genome approach. Diagnostic *in vivo* and *ex vivo* tests have not proven very useful to date in this regard. Abacavir skin-patch testing, which has 100% specificity for true immunologically mediated abacavir hypersensitivity has proved to be a useful research tool in two key clinical trials supporting the use of *HLA-B*5701* screening in clinical practice and across populations [73–77]. The understanding of the pathogenesis of abacavir hypersensitivity as an exquisitely specific *HLA-B*5701*-restricted $CD8^+$-mediated reaction also evolved concurrently with the clinical evidence that added biological plausibility and rigor to the translation of *HLA-B*5701* into the clinical setting, and added confidence that *HLA-B*5701* was in fact necessary but not sufficient for the development of abacavir hypersensitivity [85–88]. Most critical in the rollout of *HLA-B*5701* into widespread HIV clinical practice, however, was the development of cost-effective, available and internationally quality-assured laboratory testing with a user-friendly reporting format [103]. From 2005–2007, PCR-based techniques were published, including sequence-specific amplification and real-time PCR melting curve assays that could be easily applied to routine diagnostic laboratories with molecular capability [104,105]. Flow cytometricbased techniques have also been developed that fit well with other methodologically similar tests performed as part of routine HIV follow-up, such as $CD4^+$ counts, and may adapt to point-of-care testing in resource-poor settings [106]. Other laboratory tests that have been studied include a simple Taqman® (Applied Biosystems, CA, USA) assay, which detects HCP5, an endogenous retrovirus and *HLA-B*5701*-haplospecific marker, on the premise that the SNP *HCP5* rs2395029 is in complete linkage disequilibrium with *HLA-B*5701* [107]. Some caution is suggested with this approach, however, since subsequent work highlights that *HCP5* rs2395029 is in strong but not complete linkage disequilibrium with *HLA-B*5701* [108]. Cases of patch-test-positive ABC HSR that have occurred in patients positive for *HLA-B*5701* but negative for *HCP5* rs2395029 further highlight this and support the notion that it is an imperfect surrogate [88]. All evidence to date suggests that no surrogate of *HLA-B*5701* typing can be implemented, as a 100% negative predictive value must be maintained for any screening test to be safe.

Although in the current environment it seems feasible that inexpensive molecular-based tests could be developed for most pharmacogenetic markers, the full application of these tests is ultimately contingent on other issues, such as the prevalence of a gene in a given population, the number of patients it is necessary to treat to prevent one case of toxicity, characteristics of

the drug and drug toxicity, as well as the availability of evidence to support the clinical utility, cost–effectiveness and generalizability of testing across different populations [109].

For many drugs, both the prevalence of the drug hypersensitivity or related syndrome and the positive predictive value of the test are low and lead to a large number of patients needing to be tested to prevent one case of disease [109]. For the PREDICT-1 study, the positive predictive value of *HLA-B*5701*, taking a combined outcome of clinically diagnosed patch-test-positive ABC HSR, is 55%. This means that for every 100 patients screened, two or three *HLA-B*5701*-positive individuals would be excluded from abacavir that would actually have tolerated the drug. This would be balanced, however, by preventing false-positive clinical diagnosis, which occurs in at least 2–7% of patients who started abacavir therapy in the absence of screening. Differences in the number needed to test to prevent various drug hypersensitivity and related uncommon reactions such as SJS/TEN are hurdles limiting the widespread implementation of pharmacogenetics for prevention of these reactions into routine clinical practice (Tables 3 & 4).

Future perspective

Future pharmacogenomic and genetic studies in the field of drug hypersensitivity and related ‘idiosyncratic’ and immunologically mediated adverse drug reactions will be critically important, not only for identifying potential diagnostic tests that could predict and prevent these serious diseases, but also to add significant insights to the pathophysiology of these syndromes. Whole-genome studies have largely replaced candidate gene approaches; however, these have some limitations, and as with HLA associations, any associations found need to be further characterized by haplotype mapping. These approaches also have the advantage of potentially identifying specific haplotypes that increase the positive predictive value of a specific genetic test. The use of robust and well-defined phenotypes remains important for all types of pharmacogenomic/pharmacogenetic association studies. International consortia and biological data banks based on consistent definitions of disease and reproducible phenotypes will be critical to the success of pharmacogenomic work, particularly with reference to rare diseases such as SJS/TEN. Future application of pharmacogenomics will be important to screen drugs in the development phase in attempts to predict their propensity to cause Type B adverse drug reactions.

Executive summary

Drug hypersensitivity & related syndromes

- Drug hypersensitivity is a syndrome characterized by combinations of fever, rash and internal organ involvement generally occurring more than 1 week after first exposure to a drug, and is distinct from severe skin syndromes such as Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) that are characterized by blistering skin disease with mucosal and often ocular involvement that may also be associated with fever and internal organ involvement.
- Associations between HLA alleles and drug hypersensitivity and SJS/TEN hold promise that these traditionally severe and unpredictable adverse drug reactions may be predictable and preventable in the future.

Specific drug syndromes & pharmacogenetics

- For many drugs, associations between drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms and a single genetic polymorphism or *HLA* allele may not exist or may not be generalizable across diverse populations.

- Recent examples of important HLA associations include *HLA-B*5701* and abacavir hypersensitivity, *HLA-B*1502* and SJS/TEN associated with carbamazepine in Han Chinese, *HLA-B*5801* and SJS/TEN and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms associated with allopurinol, and *HLA-B*5701* and flucloxacillin drug-induced liver injury.

Translating pharmacogenetic research into clinical practice & future needs

- Pharmacogenetic studies in drug hypersensitivity and related syndromes are important not only for their potential clinical utility but also for elucidating the pathophysiological basis of these diseases.
- Implementation of *HLA-B*5701* screening for abacavir hypersensitivity has been widespread in the developing world, and serves as a roadmap to define the steps necessary to translate a test from discovery into clinical practice.
- The feasibility of applying any pharmacogenetic test to clinic practice is contingent on cost-effective and quality-assured laboratory testing with a user-friendly laboratory reporting system.
- The use of well-defined phenotypes, haplotypes and appropriate analytical approaches are critical for all types of pharmacogenetic/pharmacogenomic association studies.

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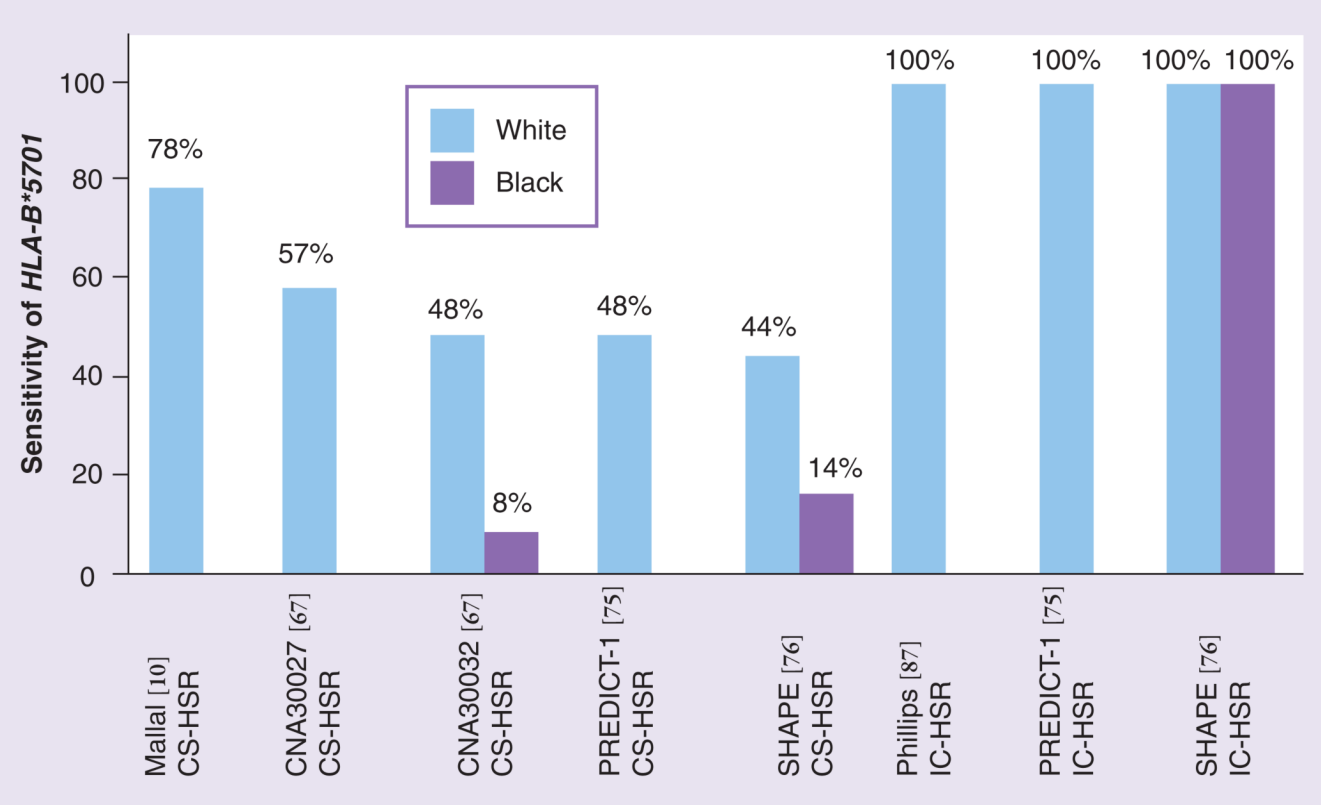

Figure 1. Sensitivity of *HLA-B*5701* for abacavir hypersensitivity

Early studies [10,67] showed low sensitivity of *HLA-B*5701* for CS ABC HSR, which was due to false-positive clinical diagnosis and was particularly apparent in black patients owing to the low carriage rate of *HLA-B*5701*. Later studies [75–76,87] that employed abacavir patch testing as a means of increasing the specificity of the diagnosis of ABC HSR showed 100% sensitivity of *HLA-B*5701* for IC (patch-test-positive) ABC HSR across both white and black populations suggesting a 100% negative predictive value of *HLA-B*5701* for ABC HSR generalizable across ethnicity.

ABC HSR: Abacavir hypersensitivity; CS: Clinically suspected; IC: Immunologically confirmed.

Table 1
Pharmacogenetics of drug hypersensitivity and related drug-induced syndromes†

Drug toxicity syndrome/drug	Allele	Ref.
Toxic epidermal necrolysis/Stevens–Johnson syndrome		
Allopurinol†	*HLA-B*5801*	[3,4]
Carbamazepine†	*HLA-B*1502*	[5–7]
Lamotrigine	*HLA-B38*	[8]
Oxicam	*HLA-B73, B12, A2*	[8,9]
Phenytoin	*HLA-B*1502*	[6,7]
Sulfonamides	*HLA-A29, -B12, -DR7*	[9]
Sulfamethoxazole	*HLA-B38*	[8]
Drug hypersensitivity/DIHS/DRESS		
Abacavir†	*HLA-B*5701*	[10,11]
Allopurinol	*HLA-B*5801*	[3]
Nevirapine		
– Rash associated hepatitis with $CD4^+$ ≥25%	*HLA-DRB1*0101*	[12]
– DIHS/DRESS in Italian population	*HLA-Cw8-B14* haplotype	[13]
– DIHS/DRESS in Japanese population	*HLA-Cw8*	[14]
– DIHS/DRESS in Thai population	*HLA-B*3505*	[15]
Carbamazepine	Promoter motilin gene (rs2894342) (Han Chinese) 8.1 ancestral haplotype (HLA-DR3-DQ2/TNF2) in Caucasians	[16] [17,18]
Delayed exanthem without systemic features		
Aminopenicillins	A2, DRw52	[19]
Carbamazepine	*HLA-A*3101* (Han Chinese)	[16]
Efavirenz	*DRB1*01*	[20]
Nevirapine	*HLA-DRB1*01* *HLA-B*3505*	[20] [15]
Drug-induced liver disease		
Amoxicillin–clavulanate	*HLA-DRB1*1501*	[21–23]
Diclofenac	*ABCB11* C-24T; *UGT2B7*2*; IL-4 C-590-A	[24]
Isoniazid	NAT2 slow acetylator, *CYP2E1*5, *1B*	[24]

Drug toxicity syndrome/drug	Allele	Ref.
Flucloxacillin	*HLA-B*5701*	[25]
Ximelagatran	*HLA-DRB1*07, -DQA1*02*	[26]
Fixed-drug eruption		
Febrazone	*HLA-B22*	[27,28]
Sulfamethoxazole	*HLA-A30–B13–Cw6* haplotype	[29]
Agranulocytosis		
Clozapine	*HLA-B38, DR4, DQw3*	[30]
Levamisole	*HLA-B27*	[31]
Drug-induced lupus erythematosis		
Hydralazine, procainamide, isoniazid, methyldopa, quinidine and others	*HLA-DR4*	[32,33]
Other drug reactions		
Aspirin (urticaria/angioedema)	*HLA-DRB1*1302–HLA-DQB1*0609–DPB1*0201* haplotype	[34]
Aspirin (asthma)	*HLA-DPB1*0301*	[35]
Gold sodium thiomalate:		
– Mucocutaneous reactions	*HLA-DR5*	[36]
– Proteinuria, thrombocytopenia or leukopenia	*HLA-B8, -DR3*	[37]
NSAIDs (anaphylactoid reaction)	*HLA-DR11*	[38]
D-enicillamine (myasthenia gravis)	*DR1*	[39]
D-penicillamine (proteinuria)	*B8, DR3*	[40]

† Odds ratio >50 and reproduced in more than one study.

DIHS: Drug-induced hypersensitivity syndrome; DRESS: Drug reaction with eosinophilia and systemic symptoms.

Adapted from [108].

Table 2

Necessary prerequisites for successful widespread integration of *HLA* pharmacogenetic testing into routine clinical care

Prerequisites	ABC	CBZ	ALL	NEV	FLUC
Test					
HLA allele is strongly associated with the toxicity and the negative predictive value of the test is high†	+++	+++	+++	++	+
The test works across different populations and ethnicities†	+++	?	?	?	?
The number of patients needed for testing to prevent a case of toxicity is low†	+++	+	+	++	-
HLA allele prevalent in a large, nondisenfranchised population†	++	+	+	++	++
Recommendation for testing incorporated into national and international treatment guidelines	+++	-	-	-	-
Recommendation for test incorporated into product monograph of drug	+++	+++	-	-	-
Drug					
Drug exhibits favorable attributes, such as good efficacy, convenience, tolerability and pill burden†	+++	+	++	++	++
Alternative drug(s) with equal efficacy that do not need pharmacogenetic testing are either absent or have negative attributes†	++	+	+++	+	++
Drug toxicity					
Toxicity can be severe and persistent† (i.e., not isolated mild rash)	++	++	++	++	++
Toxicity is readily and accurately clinically phenotyped†	+/-	++	++	+/-	++
An adjunctive diagnostic test, such as skin patch testing, can improve phenotypic precision and specificity of clinical diagnosis	+++	-	-	-	-
Environment					
Champions available (e.g., clinical academics, industry [if drug not off patent†], professional bodies, regulatory agencies, guideline committees, patient advocacy groups, laboratory providers and the media) willing and able to drive pharmacogenetic test development and implementation	+++	-	-	-	-
Generation of high level of evidence					
Case–control studies with estimated predictive values based on the assumed prevalence of the *HLA* allele	+++	++	++	-	+
Population-based cohort studies with directly calculated predictive values of the test	++	-	-	++	-
Open screening studies	+++	+	-	-	-
Supportive experimental data	+++	+	-	-	-
Blinded randomized controlled trials	+++	-	-	-	-

Prerequisites	ABC	CBZ	ALL	NEV	FLUC
Evidence across ethnic groups and geographic areas to determine the clinical settings the test may be applied to	+++	-	-	-	-
Cost–effectiveness data	++	-	-	-	-
Development & availability of appropriate laboratory support					
No patent restriction on use of the test	++	++	++	++	++
Development of simple, inexpensive, robust unambiguous allele-specific laboratory tests	+++	+	-	-	+++
Rapid and simple report and interpretation	++	-	-	-	-
Development of reagents (e.g., monoclonal antibodies and PCR-based kits)	++	-	-	-	++
Global distribution and commercialization of allele-specific test	+	-	-	-	+
Allele-specific quality assurance targeted to avoid false-negative results and consequent morbidity or mortality	+	-	-	-	+
Reimbursement of test in much of the developed world	+	-	-	-	-
Design & implementation of appropriate clinical systems					
Education of clinicians, nurses, pharmacists, phlebotomists and patients	++	-	-	-	-
Systems to ensure appropriate and routine triggering of ordering of the test	+	-	-	-	-
Systems in clinic to ensure correct blood samples are sent to the correct laboratory for analysis	+	-	-	-	-
Systems to ensure test results and correct interpretation is rapidly transmitted to, retained by and acted on by the healthcare team and patient	+	-	-	-	-

[†]Many of the necessary attributes of the test, drug, toxicity and environment are not modifiable, while other critical elements, such as a sufficient levels and types of evidence, laboratory and clinical systems, can be developed with sufficient time and resources.

+++: Prerequisite present and very strongly influential; ++: Prerequisite present and strongly influential; +: Prerequisite present and moderately influential; +/-: Prerequisite inconsistently present and dependent on external factors; -: Prerequisite absent; ABC: Abacavir/HLA-B*5701 association; ALL: Allopurinol/HLA-B*5801; CBZ: Carbamazepine/HLA-B*1502; FLUC: Flucloxacillin/HLA-B*5701; NEV: Nevirapine/HLA-DRB1*0101.

Adapted from [108].

Table 3

Number needed to test to prevent one case of drug hypersensitivity or related syndromes

Drug	*HLA* allele	*HLA* carriage rate	Prevalence of diagnosis	Negative predictive value	Approximate number needed to test to prevent '1'	Ref.
Abacavir	*B*5701*	6–8% Caucasian <1% African/Asian 2.5% African–American	8% (includes 3% true hypersensitivity and 2–7% false-positive diagnosis)	100% for patch test confirmed	13	[75]
Allopurinol	*B*5801*	9–11% Han Chinese 1–6% Caucasian	1 out of 250 to 1 out of 1000	100% in Han Chinese	250	[3]
Carbamazepine	*B *1502*	10–15% Han Chinese <0.1% Caucasian	<1–6 out of 1000	100% in Han Chinese	1000	[5]
Flucloxacillin	*B*5701*	As for abacavir	8.5 out of 100,000	99.99%	13819	[25]

The number needed to test to prevent one case of drug hypersensitivity or a related type B adverse drug reaction can have a significant impact on the feasibility of the introduction of a pharmacogenetic test into routine clinical practice. It is dependent on the prevalence of the adverse drug reaction as well as the positive predictive value of the test. Explanatory tables are shown in Table 4.

Table 4

Calculations used for number needed to test to prevent one case of drug hypersensitivity or related syndromes values

	HLA positive	HLA negative	Total	
ADR positive	a	b	a + b	Sensitivity = a/a + b × 100%
Drug tolerant	c	d	c + d	Specificity = d/c + d × 100%
Total	a + c PPV = a/a+c × 100%	b + d NPV= d/b+d × 100%	a + b + c + d = 100,000	NNT to prevent one case = 100,000/a
ABC				
	*B*5701* positive	*B*5701* negative		Prevalence of ADR = 8%
ABC-HSR (including clinical false positives)	8000	0	8000	Sensitivity = 100%
ABC tolerant	2425	89575	92000	Specificity = 97.4%
Total	10425 PPV = 76.7%	89575 NPV = 100%	100000	NNT to prevent one case = 12.5
Allopurinol				
	*B*5801* positive	*B*5801* negative		Prevalence of ADR = 4 out of 1000
Allopurinol-SJS/TEN/DIHS	400	0	400	Sensitivity = 100%
Allopurinol tolerant	14940	84660	99600	Specificity = 85%
Total	15340 PPV = 2.7%	84660 NPV = 100%	100000	NNT to prevent one case = 250
CBZ				
	*B*1502* negative	*B*1502* negative		Prevalence of ADR = 1 out of 1000
CBZ SJS	100	0	100	Sensitivity = 100%
CBZ tolerant	3000	96900	99900	Specificity = 97%
Total	3100 PPV = 3.1%	96900 NPV = 100%	100000	NNT to prevent one case = 1000
FLU				
	*B*5701* positive	*B*5701* negative		Prevalence of ADR = 8.5 out of 10.5
FLU-DILI	7.2365	1.2635	8.5	Sensitivity = 85.1%
FLU tolerant	6249.5	93742	99,991.5	Specificity = 93.8%
Total	6257 PPV = 0.11566%	93743 NPV = 99.99%	100,000	NNT to prevent one case = 13,819

The values produced from the calculations in this table are shown in Table 3.

For each drug, a theoretical population of 100,000 has been assumed, and the number of individuals with the ADR calculated based on its reported prevalence, and the number of tolerant patients calculated by subtracting this figure from 100,000. The sensitivity and specificity of the HLA test for the ADR have been taken from the literature and the numbers in each of the four cells (a, b, c and d) calculated. The positive and negative predictive values and numbers needed to test were then calculated from the numbers in each cell (a, b, c and d).

ABC HSR: Abacavir hypersensitivity; ADR: Adverse drug reaction; CBZ: Carbamazepine; DILI: Drug-induced liver injury; FLU: Flucloxacillin; NNT: Number needed to treat; NPV: Negative predictive value; PPV: Positive predictive value; SJS: Stevens–Johnson syndrome.