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Drug Hypersensitivity: Pharmacogenetics and Clinical Syndromes

Elizabeth J. Phillips, MD^{1,2,3,4}, Wen-Hung Chung, MD, PhD⁵, Maja Mockenhaupt, MD, PhD⁶, Jean-Claude Roujeau, MD⁷, and Simon A. Mallal, MB BS^{1,2}

¹Institute for Immunology & Infectious Diseases, Murdoch University

²Department of Clinical Immunology & Immunogenetics, Royal Perth Hospital

³Department of Clinical Immunology, Infectious Diseases and Clinical Pharmacology/Toxicology, Sir Charles Gairdner Hospital

⁴School of Pathology & Laboratory Medicine and Biomedical, Biomolecular and Chemical Sciences, University of Western Australia

⁵Department of Dermatology, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, 199, Tung-Hwa North Road, Taipei 105, Taiwan

⁶Department of Dermatology University Medical Center, Freiburg, Germany

⁷Department of Dermatology, Paris XII University, Créteil, France

Abstract

Severe cutaneous adverse reactions (SCARs) include syndromes such as drug reaction, eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN). An important advance has been the discovery of associations between HLA alleles and many of these syndromes including abacavir hypersensitivity reaction, allopurinol DRESS/DIHS and SJS/TEN and SJS/TEN associated with aromatic amine anticonvulsants. These HLA associations have created the promise for prevention through screening and have additionally shed further light on the immunopathogenesis of SCARs. The roll-out of HLA-B*5701 into routine clinical practice as a genetic screening test to prevent abacavir hypersensitivity provides a translational roadmap for other drugs. Numerous hurdles exist in the widespread translation of several other drugs such as carbamazepine where the positive predictive value of HLA-B*1502 is low and the negative predictive value of HLA-B*1502 for SJS/TEN may not be 100% in all ethnic groups. International collaborative consortia have been formed with the goal of developing phenotype standardization and undertaking HLA and genome-wide analyses in diverse populations with these syndromes.

Keywords

drug hypersensitivity; DRESS; DIHS; TEN/SJS; pharmacogenetics; SCAR; abacavir; nevirapine; carbamazepine; allopurinol

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Corresponding Author: Professor Elizabeth J. Phillips Institute for Immunology & Infectious Diseases Discovery Way Murdoch, Western Australia 6150 Australia Tel: +61893601385; Fax: +61893601352 e.phillips@iuid.com.au.

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Drug hypersensitivity remains an important clinical issue. It consists of a variety of phenotypes, mainly the cutaneous adverse reactions which range from milder skin reactions (e.g., exanthem, urticaria, and angioedema) to severe cutaneous adverse reactions (SCARs). SCARs are life-threatening, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS). An updated description of the clinical syndromes and pharmacogenetics of these entities as discussed during the recent DHM4 2010 in Rome, Italy is provided below.

I. Pharmacogenetics of Drug Hypersensitivity

Associations between HLA alleles and specific drug hypersensitivity syndromes such as abacavir hypersensitivity have been paradigm shifting in heralding the widespread use of a pharmacogenetic test in clinical practice to prevent the development of a specific life-threatening drug toxicity. More recently, HLA associations between DRESS/DIHS and Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN) have been described. (Table 1)^{1–20}. Identifying the true phenotypic drug hypersensitivity entity with specificity has proven to be key to identifying the pharmacogenetic markers associated with these syndromes. In the case of abacavir, this was achieved by the skin patch test which identifies patients with true immunologically mediated abacavir hypersensitivity^{21–23}. More recent work with nevirapine suggests that the specific phenotypic components of the drug hypersensitivity reaction are important for identifying specific HLA associations²⁰. The association between the class I, major histocompatibility allele, HLA-B*5701 and abacavir hypersensitivity has also furthered our understanding of the immunopathogenesis of this and other drug reactions and has provided a roadmap from discovery to widespread implementation of a pharmacogenetic association²⁴. Most work currently has focused on the pharmacogenetics of drug hypersensitivity syndromes and SJS/TEN of drugs such as abacavir, nevirapine, anticonvulsants and allopurinol. Further work and international collaborations will be needed to determine the pharmacogenetic basis of other drugs and reactions such as IgE mediated reactions and other syndromes such as acute generalized exanthematous pustulosis.

Abacavir

The pathway from discovery of a pharmacogenetic association to widespread clinical implementation is not without significant hurdles as illustrated by the “abacavir example”. Abacavir, an antiretroviral drug FDA approved for use since 1998 was known to be associated with a drug hypersensitivity syndrome in approximately 8% of those starting the drug. In 2002, two groups independently published a strong association between HLA-B*5701 and abacavir hypersensitivity^{12,13}. Early doubts as to the widespread applicability of HLA-B*5701 as a potential routine screening test to prevent abacavir hypersensitivity were raised based on an apparent low sensitivity in Black and Hispanic populations that have a much lower carriage rate of HLA-B*5701²⁵. This apparent low sensitivity was actually the result of a high rate of clinical false-positive diagnosis in these populations with a low prevalence of HLA-B*5701 and this is highlighted in abacavir double-blind randomized clinical trials where up to 7% of patients not receiving abacavir had a clinical diagnosis of abacavir hypersensitivity²⁴. To overcome this problem of false positive clinical diagnosis, abacavir patch testing was used as a specific test to identify true immunologically mediated abacavir hypersensitivity^{21–23}. Two clinical trials, the PREDICT-1 and SHAPE studies incorporated skin patching into their study design as a way of identifying the true phenotype of abacavir hypersensitivity^{14,15}. The PREDICT-1 study was the first randomized double-blind controlled study to prospectively test the clinical utility of a pharmacogenetic test to prevent a specific toxicity. This study which enrolled 84%

Caucasians, was compelling in showing a 100% negative predictive value of HLA-B*5701 as a screening test for the prevention of abacavir hypersensitivity¹⁴. The SHAPE study was a case-control study enrolling both Black and White American patients that suggested a 100% negative predictive value of HLA-B*5701 for abacavir hypersensitivity generalizable across Black and White race¹⁵. Additional evidence from observational studies from different centres suggested HLA-B*5701 screening to be cost-effective in “real clinical practice” not only by eliminating true immunologically mediated abacavir hypersensitivity but also by reducing false positive clinical diagnosis²⁴. The abacavir story provides a translational roadmap from the discovery of a genetic association through to implementation of a pharmacogenetic test in routine clinical care (Figure 1). In addition, important lessons were gleaned from abacavir clinical trials that can be applied to other drugs and pharmacogenetic markers. The PREDICT-1 study illustrated that using co-primary endpoints, where one was sensitive and not specific (clinical diagnosis) and the other was specific and not 100% sensitive (patch testing) was a powerful tool. The validation of a simple, inexpensive, allele specific molecular test against the gold standard of high resolution full allelic HLA typing in the PREDICT-1 study was also crucial to the widespread implementation of cost-effective and feasible methods for HLA-B*5701 screening. The abacavir story also clearly illustrated that any randomized controlled trial aiming to study the clinical utility of a pharmacogenetic marker to prevent a specific toxicity must look at the dominant ethnic group. Case control studies, such as the SHAPE study, on the other hand are most ideally used to generalize the results from the dominant ethnic group to other groups with low prevalence of the allele in question. Finally observational and open screening studies are useful to define the role, practical issues surrounding implementation, and benefits of genetic testing in real clinical practice and can sometimes pick out different effects such as the decrease in false positive clinical diagnosis in addition to decreasing the rates of true hypersensitivity in the case of abacavir. Much of the success of the implementation of HLA-B*5701 testing in clinical practice relates to the 100% negative predictive value of this pharmacogenetic marker as well as the high (55%) positive predictive value¹⁴. Taking into account the high rates of false positive diagnosis this means that only 13 subjects would need to be screened to prevent one case of hypersensitivity²⁴. Although many other HLA alleles associated with specific drug-induced diseases share a 100% or close to 100% negative predictive value, the positive predictive value and the prevalence of these diseases is much lower, creating challenges from the large number that would be needed to test to prevent one case (Figure 2).

Nevirapine

Nevirapine is a nonnucleoside reverse transcriptase inhibitor used in the combination treatment of patients with HIV-1 infection and is associated with a drug hypersensitivity syndrome in approximately 5% of those starting the drug and SJS/TEN in 0.3% or less of those initiating the drug²⁴. Nevirapine differs from abacavir in that distinct class I and II associations have been described in association with nevirapine rash and hypersensitivity across different populations. A population based study from Western Australia associated the MHC Class II allele HLA-DRB1*0101 with rash associated hepatitis in those with a CD4% ≥ 25 ¹⁶. This clinical work has been supported by ex vivo studies suggesting that nevirapine hypersensitivity is a CD4 cell dependent process²⁴. Another case-control study in a Thai population associated nevirapine rash and hypersensitivity with HLA-B*3505 which was present in 17.5% of HIV patients with nevirapine rash or hypersensitivity versus 1.1% of nevirapine tolerant controls and < 1% of the general Thai population¹⁹. This same group is attempting to validate findings through a prospective blinded randomized screening study where subjects randomized to the HLA-B*3505 testing arm will be excluded from nevirapine if positive²⁶. Additional studies have associated MHC Class I alleles with nevirapine hypersensitivity such as HLA-B*1402 and HLA-Cw8 in a Sardinian population

and HLA-Cw8 in a Japanese population^{17,18}. Although familial occurrence of SJS/TEN associated with nevirapine has been described, suggesting a genetic basis, no HLA or genetic basis has currently been determined²⁴. An updated analysis of the Western Australia cohort by Phillips (Perth, Australia) gives further insights into the potential pharmacogenetic basis of nevirapine hypersensitivity²⁰. In this study the original association between HLA-DRB1*0101 and CD4% ≥ 25 and nevirapine hypersensitivity with hepatitis held up however a new association was found between HLA-B*3501 and nevirapine hypersensitivity with rash²⁰. In addition it appears that the phenotype of the drug hypersensitivity syndrome may be critical when attempting to delineate HLA associations. For instance HLA-DRB1*0101 was associated with rash only in the presence of hepatitis²⁰. Specific HLA-B and DR pairings appeared to be important for the hepatitis phenotype and HLA-B for the rash phenotype. This could shed important light not only on the approach to studying the pharmacogenetics of drug hypersensitivity syndromes as well as the cellular and immunopathogenetic basis of these drug-induced diseases. Various HLA-B types that have been associated with SJS/TEN and/or drug hypersensitivity syndromes such as allopurinol and HLA-B*5801, carbamazepine(CBZ) and HLA-B*1502, HLA-B*5701 and abacavir hypersensitivity and flucloxacillin hepatotoxicity and nevirapine hypersensitivity and HLA-B*3505/01. It is intriguing that all of these HLA types share a similar chemistry of the F pocket of HLA-B with a serine at position 116 which may explain the propensity of haptenated peptides to bind²⁰.

II. Pharmacogenetics of Other Severe Cutaneous Adverse Reactions

Severe Cutaneous Adverse Reactions, Clinical Syndromes, and the RegiSCAR group

Adverse drug reactions affecting the skin are frequent and they present with a large variety of phenotypes. The term SCAR (Severe Cutaneous Adverse Reactions) was proposed for very rare reactions that are associated with a significant morbidity and mortality, non-predictable (idiosyncratic, and likely resulting from immunological mechanisms) and most often induced by drugs. A multinational collaborative research team was established in 1988 to study SCAR bringing together dermatologists, epidemiologists, geneticists, immunologists and pharmacologists^{27,28}. It changed its name from SCAR-group to EUROSCAR-and lately RegiSCAR when enlarging the scope of diseases of interest and aggregating new participating teams. At present the RegiSCAR-group is active in Austria, France, Germany, Italy, The Netherlands, South Africa, Taiwan and the United Kingdom and should soon include several new European countries. It is operating as a registry collecting detailed clinical data and biological samples on 3 varieties of SCAR: 1) SJS/TEN 2) DRESS/DIHS and 3) Acute Generalized Exanthematous Pustulosis(AGEP).

The group defined consensus diagnosis criteria for each type of SCAR^{29–31}. Potential cases of SCAR are detected in a large network of participating hospitals and investigated by direct interviews using standardized questionnaires to collect detailed information on phenotype of the reaction (that includes clinical photographs and skin biopsies in most cases), associated conditions and exposure to medications. Potential cases are validated by an “expert committee” blinded for risk factors, including medications. Using this strict methodology the group collected and curated detailed quality data on more than 1000 cases of SJS/TEN in Europe. A case-control analysis indicated that a dozen “high risk” medications accounted for more than one half of cases²⁸. During the course of these studies it became evident that misdiagnoses were frequent, drug exposure was incompletely ascertained by reporting physicians making it difficult to attribute causality to a particular drug. These findings point to the advantage of direct interviews with patients and relatives and of structured and systematic questioning on drug use. The follow-up of a large cohort of patients with SJS/TEN has also shown that mortality and prevalence of severe sequelae were higher than previously suspected.

These studies show that “undetermined” or “overlapping” cases of SCAR were rare if clear diagnostic criteria and a rigorous systemic approach to phenotyping was used. It also established that SJS and TEN should be considered as severity variants of a single disease, distinct from Erythema exsudativum multiforme majus which has different demographic characteristics of patients, associated diseases, severity, causality and prognosis³². Hashimoto (Ehime, Japan) presented new data to suggest that rarely overlap can occur between SJS/TEN and DRESS/DIHS. For the most part, however, SJS/TEN and DRESS are now thought to be distinct entities, though many of the same “high risk” drugs have been implicated to precipitate the two syndromes³³.

Backgrounds and progress in pharmacogenetics of SCARs in Han Chinese

Although the incidences of SCARs are low, their complications and sequelae can result in death or disability in formerly healthy people^{28,34}. Several drugs have been withdrawn from the market because of their association with SCARs³⁵. The culprit drugs associated with SCARs are distinct in different countries^{28,34,36}. CBZ and allopurinol were two of the most common agents causing SJS and TEN in Taiwan, where Han Chinese forms the largest ethnic group and makes up ~98% of the population^{1, 36}. HLA-B*1502 was initially found to be a genetic marker for CBZ-induced SJS/TEN in Han Chinese⁵, and this association has subsequently been found to be phenotype-specific as the HLA-B*1502 allele has shown no association with non-blistering cutaneous reactions, such as exanthem or DRESS. What was described as CBZ-induced maculopapular exanthem was associated with HLA-A*3101 in Han Chinese³⁷. Recently, HLA-B*1502 was found to be associated with an increased risk of SJS/TEN on exposure to aromatic antiepileptic drugs, including phenytoin, oxcarbamazepine and potentially lamotrigine; although the strength of these associations were weaker than that of CBZ¹¹. Previous work in Han Chinese also identified that HLA-B*5801 allele is a genetic marker for SJS/TEN/DRESS induced by allopurinol, a commonly prescribed medication for gout and hyperuricemia.¹. These data suggested that genetic susceptibility to drug hypersensitivity is both phenotype- and drug-specific.

Progress of pharmacogenetics of SCARs in other countries

In 2006, researchers of Regi-SCAR group confirmed the same link between HLA-B*1502 and CBZ-SJS/TEN in four European inhabitants who were born in Asian countries. However, this association was not found in Caucasian patients of CBZ-SJS/TEN^{4,38}. Man *et al.* enrolled Han Chinese living in Hong Kong, and validated that HLA-B*1502 was associated with SCARs induced by CBZ, phenytoin, and potentially lamotrigine⁶. Two studies from Thailand replicated the strong association between HLA-B*1502 allele and patients with CBZ-SJS/TEN^{3,7}. In addition, Chang *et al.* reported that up to 75% of patients with CBZ-SJS/TEN were the carriers of HLA-B*1502 in Malaysia, a country composed of four races, with the majority Malay and Han Chinese showing carriage frequencies of HLA-B*1502 of 15.7% and 5.7%, respectively⁸. A recent study from India showed 6 out of 8 (75%) CBZ-SJS patients were positive for HLA-B*1502 allele, with an average HLA-B*1502 carriage frequency of 2.5% in the general population⁹. By comparison, the same association was not found in the study populations from Japan, where the allele frequency of HLA-B*1502 is very low (less than 0.1%)^{2,10}. Ikezawa (Yokohama, Japan) reported that CBZ-SJS/TEN in Japan was associated with HLA-B*1511, a member of HLA-B*75 type that also includes HLA-B*1502, B*1508, B*1521, B*1530 and *1531. These data suggested that not only HLA-B*1502, but also the other HLA-B*75 members are risk factors for CBZ-induced SJS/TEN in Asians. In addition, the association between HLA-B*5801 and allopurinol-SJS/TEN/DRESS has been validated in different populations, including Japanese, European, and Thai people^{2-4,38}. It is interesting to note that the strength of genetic associations that have been found relate to the prevalence of the susceptibility allele in the ethnic populations with consistent results in Southeast and South

Asia, where the frequencies of the risk alleles are higher. US FDA and regulatory agencies in some other countries have modified the drug label or product information⁴¹. For example screening for HLA-B*1502 before prescribing CBZ is recommended for individuals of Asian ancestry, particularly for those of Southeast Asian ancestry.

Regiscar studies on pharmacogenetics and pharmacogenetics of SCAR in Europe

Since 2003 RegiSCAR has collected biological samples of patients with SCAR to allow future studies on the mechanisms and genetics of these reactions. The collection was assembled in compliance with existing regulations, approved by relevant ethical committees and all patients provided a signed informed consent. Samples were recoded by a professional blood bank and correlation between de-identified data on phenotype and samples was strictly protected and only accessible to the data center after formal agreement of the steering committee of RegiSCAR.

RegiSCAR initially took a candidate gene approach focusing on “usual suspects” according to present knowledge or hypotheses of the physiopathology of SCAR. It is known that massive apoptosis of keratinocytes follows invasion by drug-specific cytotoxic T-cells and NK cells and release of a variety of cytokines. Reactive metabolites may initiate the immune response although it is also possible that the parent molecule directly interacts with the MHCTcR to initiate the immune response (pharmacological interaction of drugs with immune receptors; “the P-I concept”). The list of “candidate genes” included the genes related to the polymorphism of metabolizing enzymes, genes contributing to the regulation of immune response (including HLA region), and genes related to apoptosis (such as death messengers and receptor and caspases).

The 2004 and 2005 publications by the Taiwanese group reported very strong associations between HLA and SCAR (HLA-B*1502 and CBZ related SJS/TEN; B*5801 and allopurinol related SCAR). This prompted RegiSCAR to look for HLA associations in European subgroups of SJS/TEN cases induced by “high risk” medications. These studies³⁸ were disappointing in that an association could not be detected between CBZ related cases in patients from European descent and HLA-B*1502, or with another HLA allele. HLA-B*5801 was associated with allopurinol related SJS/TEN in European patients, but only had a 60% sensitivity instead of the 100% sensitivity reported in Taiwan⁴. For other high risk drugs a few, very rare alleles were found significantly associated, but the sensitivity of these tests were so low that it is very unlikely that any will be applied clinically.

The comparison of the European results with the findings from Taiwan has yielded interesting findings and conclusions with regards to CBZ associated SJS and TEN which occurs at a much lower prevalence (1/10,000) in Caucasian populations. In Europe, where the prevalence of B*1502 is very low (< 0.1%), although HLA-B*1502 appears the strongest genetic risk factor for SJS/TEN, it lacks sensitivity. Other HLA alleles may yet be implicated in pathogenesis of CBZ-induced SJS/TEN in non-Asian populations.

The above considerations led the RegiSCAR group to collaborate with the Centre National du Genotypage (Evry, France) in a Genome Wide Association Study using Illumina 317K chips. As presented by Mockenhaupt (Freiburg, Germany) over 600 validated cases of SJS or TEN enrolled by RegiSCAR in six countries with a majority in France and Germany, adequate amounts of DNA were available in 563 cases (226 males and 337 females). Several SNPs all located in the HLA region on chromosome 6 were found significantly associated with p-values of < 10⁻⁶. The most significantly associated SNP was located close the HLA-B locus. The association was much stronger in patients exposed to allopurinol than in those exposed to other drugs but remained significant after exclusion of all cases exposed to allopurinol. The involvement of genetic variants located in the HLA region in SJS/TEN was

therefore confirmed in European cases, especially in association with allopurinol as previously demonstrated by HLA studies⁴. No other locus reached genome-wide association criteria in this study.

This sample of SJS/TEN cases was the largest one collected so far. It is thus unlikely that in European populations any “high risk drug” will have an association with a specific common allele strong enough to be useful as a predictive marker.

The probability that further studies on the genetics of SJS/TEN will find associations not detected in a European population by the RegiSCAR GWAS study is low, unless if performed in homogeneous ethnic groups with a “high” prevalence of reaction to a given medication.

Functional studies and pathogenesis of SCARs in relation the pharmacogenetics

Hung (Taipei, Taiwan) proposed that the specific HLA-B allele is not only a genetic marker for SCARs, but also plays functional roles in the pathogenesis of the diseases. By *in vitro* assay, Hung (Taipei, Taiwan) showed that HLA-B*1502 is specific for the CBZ binding to activate CTLs of CBZ-SJS/TEN patients. Upon the stimulation, CTLs expressed a large amount of granulysin which was identified as a key mediator responsible for the extensive epidermal necrolysis in SJS/TEN. Chung (Taipeh, Taiwan) presented intriguing data to suggest that granulysin produced by the CTLs and NK cells, causes widespread keratinocyte death, is a prognostic biomarker for SJS/TEN, and may be useful as a therapeutic target for developing new methods for the treatment of SJS/TEN⁴¹. These studies of genetics, epidemiology, and immunological mechanisms of SJS/TEN are improving our understanding of drug hypersensitivity and having practical impact in the clinic.

Other findings and future directions

Mallal (Perth, Australia) reviewed the abacavir example and that HLA-B*5701 screening for abacavir has been a success story that has created a translational roadmap for other drugs²⁴ (Figure 1). Important elements driving this success have been cost-effective, simplified and feasible methods for HLA-B*5701 screening and an accompanying international quality assurance program. The generation of evidence that HLA-B*5701 has 100% negative predictive value for abacavir hypersensitivity generalizable across race was key to the routine clinical implementation of this test. The high positive predictive value and the low numbers of subjects needed to test to prevent one case of abacavir hypersensitivity have also contributed to the feasibility and cost-effectiveness of HLA-B*5701 testing (Figure 2). The implementation of other predictive pharmacogenetic markers into clinical practice may be more challenging and population dependent. A large observational prospective study employing HLA-B*1502 screening in patients being initiated on CBZ was conducted in 25 hospitals in Taiwan and has now enrolled over 4000 patients. This study incorporated a allele specific PCR-based test for HLA-B*1502 with a turn around time of three days⁴². Chen (Taipeh, Taiwan) presented an updated analysis of this study, and no patients in this study developed SJS/TEN compared with 8 cases in a historical control group (0.25%). Little information was gained from this study with regards to reactions associated with potentially cross-reactive aromatic amine anticonvulsants such as phenytoin, where SJS/TEN also appear to be HLA-B*1502 associated. Even in higher prevalence groups such as Han Chinese, the positive predictive value of HLA-B*1502 for CBZ-induced SJS/TEN appears to be low (Figure 2). Chen and Hung (Taipeh, Taiwan) presented further evidence to suggest that specific V β ₁₁ T cell receptor clonotypes may be necessary to evoke the T-cell responses leading to the phenotype of SJS/TEN in HLA-B*1502 positive individuals. FDA recommendation to test for HLA B*1502 persons from Asian ancestry before prescribing CBZ may be useful only for persons of Chinese and Southern Asian

origin. Importantly, the CBZ example illustrates that unlike abacavir, the 100% negative predictive value of HLA-B*1502 for SJS/TEN in Han Chinese and some other Asian groups appears not to be generalizable to Caucasians, as demonstrated by European cases of CBZ-associated SJS/TEN lacking HLA-B*1502³⁸. Since 2010 in Taiwan, the national health insurance has covered the expense of the genetic screening for HLA-B*1502 in individuals initiating CBZ. In the case of allopurinol, in Europe a prior RegiSCAR study⁴³ showed that the majority of allopurinol attributed cases of SJS/TEN were related to inappropriate use. Decreasing inappropriate use of allopurinol by reinforcing prescription rules may be an additional strategy to prevent SCAR related to allopurinol in European populations.

To-date most pharmacogenetic associations described have related to delayed reactions such as drug hypersensitivity syndromes and SJS/TEN. Much less knowledge exists regarding the pharmacogenetics of IgE-mediated reactions such as occur with beta-lactam antimicrobials which was reviewed by Gueant (Nancy, France). For these reactions there is the additional challenge of defining a durable phenotype as is known that IgE reactivity can wane and disappear over the course of a lifetime. This is particularly known to occur with penicillin, where approximately 10% of patient per year will lose skin test reactivity and the positive predictive value of testing is 50–60%. Specific HLA associations have not been described in association with IgE mediated reactions such as beta-lactam allergy. However genes related to atopy and IgE production such as IL-4, IL-4RA, IL-13 and TNF- α have been examined, with specific polymorphisms of these genes associating with risk of beta-lactam allergy as defined by clinical presentation and/or skin test positivity in case control studies^{44–47}.

The future of defining the pharmacogenetic basis of the full spectrum of immunologically mediated drug reactions, will rest on international collaborative efforts to gather well phenotyped cases for specific drugs and specific drug reactions and apply broad approaches such as high resolution HLA typing followed by whole genome analysis and/or new technologies as they become available. As reinforced by Mockenjaupt (Freiburg, Germany), Roujeau (Creteil, France) and Shear (Toronto, Canada), registries such as RegiSCAR, and the newly formed International Consortium on Drug Hypersensitivity (ITCH) are making important progress in this regard. Although an understanding of the pharmacogenetic basis for these reactions will not inevitably translate into clinically useful genetic markers for the majority of drugs, it will provide valuable insights into the immunopathogenesis of these reactions.

Capsule Summary

Improved phenotyping of drug hypersensitivity syndromes in the era of high resolution HLA-typing has yielded some striking pharmacogenetic associations and insights into the successful translation of pharmacogenetics into the clinic.

Abbreviations

DRESS	drug reaction eosinophilia systemic symptoms
DIHS	drug-induced hypersensitivity syndrome
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
CBZ	carbamazepine
CTL	cytotoxic T-lymphocytes
NK	natural killer

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Figure 1.
Translational Roadmap from Discovery of HLA-B*5701 Association with Abacavir Hypersensitivity to Widespread Clinical Implementation

Drug	HLA Allele	Prevalence of Allele	Prevalence of Reaction	Relative Risk	Number Needed to Test (NNT)
Abacavir	HLA-B*57:01	6.5%	6% (SJS/TEN)	1000	17
Allopurinol	HLA-B*58:01	0.5%	0.1% (SJS/TEN)	1000	200
Carbamazepine	HLA-A*31:01	0.1%	0.1% (SJS/TEN)	1000	1000
Flucloxacillin	HLA-B*57:01	6.5%	0.1% (DILI)	1000	1000

Figure 2.

Number needed to test (NNT) to prevent one case of specific drug reaction. Numbers shown are for abacavir hypersensitivity, allopurinol associated SJS/TEN/drug hypersensitivity, carbamazepine associated SJS/TEN and flucloxacillin associated drug induced liver disease. Adapted from Phillips E, Pharmacogenomics 2010 ref 24.

Table 1

Recent HLA Associations with DIHS/DRESS and SJS/TEN

Drug toxicity syndrome/Drug	Ethnicity	Allele	Ref
SJS/TEN			
Allopurinol	Han Chinese,	HLA-B*5801	1
	Japanese		2
	Thai		3
	Caucasians		4
Carbamazepine	Han Chinese, Thai	HLA-B*1502	5,6,7
	Malaysians		8
	Indian		9
	Japanese	HLA-B*1511; HLA-B*5901	Ikezawa (Yokohama) 10
Oxcarbamazepine	Han Chinese,	HLA-B*1502	11
Phenytoin	Han Chinese, Thai	HLA-B*1502	6
DIHS/DRESS			
Abacavir	Highest risk in Caucasians but generalizable across ethnicity	HLA-B*5701	12 – 15
Allopurinol	Han Chinese	HLA-B*5801	1
Nevirapine-rash associated hepatitis with CD4+ ≥25%	Caucasian	HLA-DRB1*0101	16
-DIHS/DRESS	Sardinian	HLA-Cw8-B14 haplotype	17
-DIHS/DRESS	Japanese	HLA-Cw8	18
-DIHS/DRESS with rash (no liver function tests done)	Thai	HLA-B*3505	19
-DIHS/DRESS with rash	Caucasian	HLA-B*3501	20