New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity

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Drug hypersensitivity reactions are an important clinical problem for both health care and industry. Recent advances in genetics have identified a number of HLA alleles associated with a range of these adverse reactions predominantly affecting the skin but also other organs, such as the liver. The associations between abacavir hypersensitivity and *HLA-B*57:01* and carbamazepine-induced Stevens-Johnson syndrome and *HLA-B*15:02* have been implemented in clinical practice. There are many different mechanisms proposed in the pathogenesis of drug hypersensitivity reactions, including the hapten hypothesis, direct binding to T-cell receptors (the pharmacologic interaction hypothesis), and peptide-binding displacement. A problem with all the hypotheses is that they are largely based on *in vitro* findings, with little direct *in vivo* evidence. Although most studies have focused on individual mechanisms, it is perhaps more important to consider them all as being complementary, potentially occurring at the same time with the same drug in the same patient. This might at least partly account for the heterogeneity of the immune response seen in different patients. There is a need to develop novel methodologies to evaluate how the *in vitro* mechanisms relate to the *in vivo* situation and how the highly consistent genetic findings with different HLA alleles can be more consistently used for both prediction and prevention of these serious adverse reactions. (J Allergy Clin Immunol 2015;136:236-44.)

Key words: *Drug hypersensitivity, HLA, genetic polymorphisms, mechanisms, crystallography*

Abbreviations used
ADR: Adverse drug reaction
p-i: Pharmacologic interaction
SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis

Adverse drug reactions (ADRs) remain a major problem in the clinic and in drug development.[1] Of particular concern are unpredictable ADRs, which are often referred to as type B or idiosyncratic reactions.[2] They can affect any organ system, most commonly the skin but also the liver, lungs, bone marrow, and kidneys. Such reactions are still poorly understood, but many of them are often assumed to be immunologic in nature,[3] so-called drug hypersensitivity reactions.

Recent advances in the pharmacogenetics of drug hypersensitivity reactions, most notably HLA restriction, have provided persuasive evidence that some of these drug reactions have an immunologic component. Furthermore, such advances are beginning to provide the experimental tools to investigate the interplay between the genetic, cellular, and chemical mechanisms postulated to be involved in drug hypersensitivity. We now need to build on such advances in a critical and constructive fashion to:

- develop diagnostic tests to define whether an ADR to a new drug is truly immunologic;
- develop pharmacogenetics tests (which might be point of care) for patients to prevent these reactions, which would fit in with the evolving paradigm of personalized or precision medicine; and
- provide the science to develop novel *in vitro* model systems with which to (1) eliminate immunologic liabilities from drugs known to be associated with hypersensitivity and (2) develop preclinical test systems to minimize the immunologic liabilities of new drugs in development.

To achieve these goals, we need to investigate further the best understood case histories "from man to molecule and back again."

GENETIC BASIS OF DRUG HYPERSENSITIVITY

Association with HLA alleles

Since the completion of the human genome project, there have been some remarkable advances in elucidating the genetic basis of drug hypersensitivity reactions.[4,5] This has largely focused on the HLA alleles in the MHC on the short arm of chromosome 6.

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Both M.P. and B.K.P. wish to thank the MRC for their support through the MRC Centre for Drug Safety Science. M.P. is a NIHR Senior Investigator. D.A.O. is supported through National Institutes of Health/National Institute of Allergy and Infectious Diseases grant 5R01AI103348-02.

Disclosure of potential conflict of interest: M. Pirmohamed has received research support from the Medical Research Council and the National Institute for Health Research. D. A. Ostrov has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (R01 AI103348). B. K. Park declares that he has no relevant conflicts of interest.

Received for publication May 18, 2015; revised June 22, 2015; accepted for publication June 23, 2015.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2015.06.022

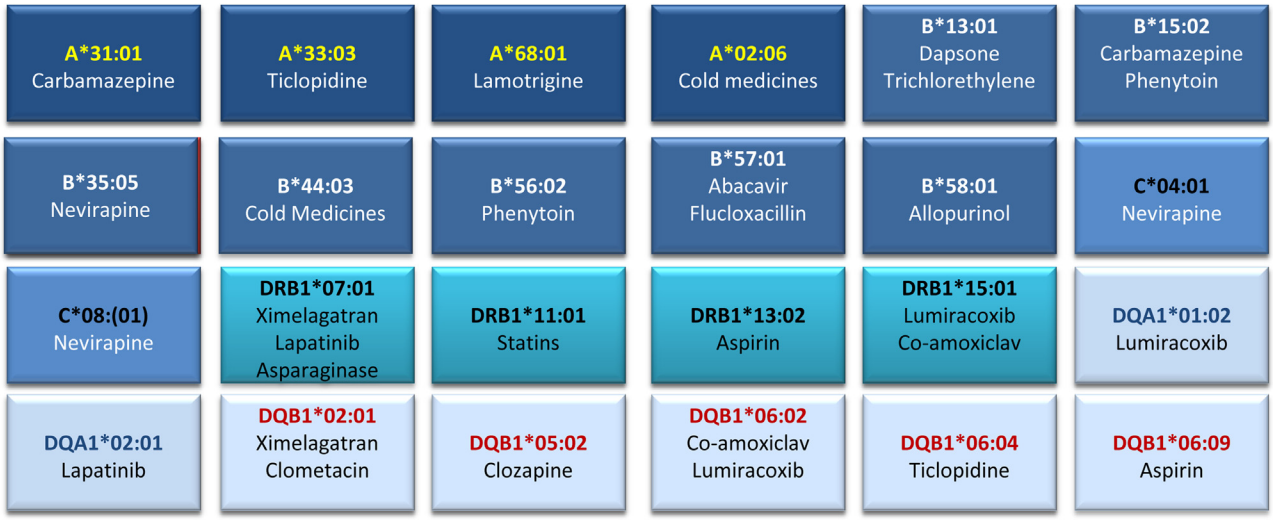

FIG 1. HLA associations reported with serious ADRs caused by many different drugs. This is not an exhaustive list of reported drug-HLA associations but illustrates that the pattern of drug–HLA–tissue injury interactions varies and that there is no general rule for predicting susceptibility.

This is the region of the genome that is highly polymorphic and has been linked to both autoimmune diseases and infectious diseases. Since 2001, at least 24 ADRs have been linked to different HLA alleles (Fig 1). These associations afford a fascinating insight into the complexity of the immune response, highlighting our incomplete understanding of the pathogenesis of these reactions. However, they also provide several important insights that need to be addressed in future research.

First, different organ systems are affected by these ADRs, most commonly the skin and liver, but also muscles (statin-induced autoimmune myopathy and *HLA-DRB1*11:01*)[6] and neutrophils (clozapine-induced agranulocytosis and *HLA-DQB1*).[7] Whether the HLA allele determines which organ system is affected is unclear, but it is likely to play a role in association with other factors, such as other genetic variants, expression of organ-homing receptors, and T-cell clonotypes.

Second, the associations sometimes show marked ethnic variation reflecting the background prevalence of the implicated HLA allele. The most impressive example of this is the association of *HLA-B*15:02* with carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Han Chinese, Thai, and Malay patients[8] but not in Northern Europeans.[9] The background prevalence of *HLA-B*15:02* varies from 4% to 15% in the affected populations but is less than 1% in Japanese and Korean subjects and extremely rare in Northern Europeans (<0.01%).

Third, the same HLA allele can be associated with adverse reactions to therapeutically and structurally unrelated compounds but with effects in different organs. The best example of this is the association of *HLA-B*57:01* with both abacavir hypersensitivity[10] and flucloxacillin-induced hepatotoxicity.[11] This is considered in more detail below.

Fourth, the same type of organ injury can occur with the same HLA allele, even with therapeutically and structurally unrelated compounds. For example, *HLA-DRB1*15:01* is associated with liver injury with both lumiracoxib[12] and co-amoxiclav.[13] Whether there are some HLA alleles that predispose to certain forms of organ injury will become clear as more research is undertaken with other drugs but seems likely based on the possibility that certain HLA alleles can be more highly expressed in particular organs. Consistent with this, a recent genome-wide association study showed that *HLA-DRB1*15:01* is also associated with alcohol-induced liver cirrhosis.[14]

Fifth, although most of the associations illustrated in Fig 1 are consistent with the time lag needed to induce an immune response (and are consistent with clinical and histologic evidence), for some forms of organ injury, the HLA association was surprising and highlighted that the general rules of immune-mediated injury occurring soon after the start of the drug or being worse on rechallenge are not necessarily correct in all cases. For example, lumiracoxib-induced liver injury typically occurs after more than 100 days on the drug[12] which is not the usual timeframe associated with liver injury caused by other drugs, such as co-amoxiclav. For clozapine agranulocytosis, rechallenge does not necessarily result in recurrence of the reaction much sooner,[15] which is inconsistent with evidence from other forms of immune-mediated drug injury, such as abacavir hypersensitivity.[16]

Finally, it is interesting to note that the drugs most commonly associated with cutaneous ADRs, such as the penicillins and sulfonamides, have not convincingly been shown to have associations with HLA alleles. This might be because they form multiple epitopes and therefore interact with multiple HLA alleles, but this cannot be the full explanation given the very strong association between flucloxacillin hepatotoxicity and *HLA-B*57:01*. A possible explanation is that studies thus far have not phenotyped the patients precisely with mixing of phenotypes, poor assessment of causality, and inadequate sample sizes. This is perhaps illustrated by a recent genome-wide study in which careful phenotyping of an adequate number of patients with penicillin-induced type 1 IgE-mediated reactions showed an association within the *HLA-DRA* region.[17]

Association with non-HLA alleles

Observational studies have shown with some drugs, such as phenytoin, that higher doses, particularly at commencement, can increase the risk of cutaneous eruptions.[18] Similarly, with lamotrigine, higher doses, particularly when the patient is cotreated with