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Pharmacogenomic Biomarkers for Prediction of Severe Adverse Drug Reactions

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The accumulating knowledge of human genomic variation is being used for the development of personalized medicine, with the aims of decreasing the number of adverse drug reactions and increasing the efficacy of drug treatment. Considerable pharmacogenomic research has focused on understanding the molecular mechanisms behind adverse drug reactions and finding biomarkers that identify people at risk.

Serious adverse drug reactions have been shown to cause or contribute to 6 to 7% of all hospitalizations, a 2-day increase in the average length of hospitalization, and 100,000 deaths annually in the United States — and may, according to some estimates, cost about as much as the drug treatment itself.¹ During the period 1998–2005, the numbers of reported adverse drug reactions and deaths related to such reactions have increased, both by a factor of about 2.6.² Adverse drug reactions are also a major problem during the development of a drug. In total, approximately 4% of all new medical agents are withdrawn from the market owing to adverse drug reactions.¹ During the period 1995–2005, at least 34 drugs were withdrawn, mainly as a result of hepatotoxic or cardiotoxic effects — notably, cerivastatin, nefazodone, rofecoxib (Vioxx), terfenadine, and troglitazone.³

The search for pharmacogenomic biomarkers that could be used to identify patients at increased risk for drug-related toxic effects has often focused on variation within genes encoding drug-metabolizing enzymes. Altered enzymatic activity can lead to elevated levels of the substrate drug, or alternatively, increased amounts of a reactive metabolite, either of which could have toxic effects.

For immune-mediated toxic effects, much focus has been placed on the major-histocompatibility-complex class I genes. A review of pharmacogenomic biomarkers reveals only a limited number of potentially useful examples (Table 1), with the highest specificity seen among the HLA allelic variants. Thus, many more biomarkers remain to be identified. Unfortunately, much of the existing research in this area has been hampered by limitations in study design, such as poorly defined case and control groups, the use of retrospective and nonblind study protocols, and nonoptimal selection of gene variants. In addition, polygenic influences on many adverse drug reactions, instances of treatment with multiple drugs, and variation in the severity of clinical

Table 1. Pharmacogenomic Biomarkers as Predictors of Adverse Drug Reactions.

Gene or Allele	Relevant Drug	Specificity of Biomarker	Percent of Patients with an Adverse Reaction to Drug*
TPMT (mutant)	6-Mercaptopurines	Very good	1–10
UGT1A1*28	Irinotecan	Good	30–40
CYP2C9 and VKORC1	Warfarin†	Good	5–40
CYP2D6 (mutant)	Tricyclic anti-depressants	Relatively good	5–7
HLA-B*5701	Abacavir	Very good	5–8
HLA-B*1502	Carbamazepine	Very good	10
HLA-DRB1*07 and DQA1*02	Ximelagatran	Good	5–7

* Percentages are of affected whites except that for HLA-B*1502, which is the percentage of affected Asians.

† Carriage of the CYP2C9 and VKORC1 alleles affects warfarin dosing.

cally observed reactions make gene identification difficult. As a result, only a limited number of reports of a positive association between genetic characteristics and adverse drug reactions have been reproduced.⁴ There is therefore a great need for large, randomized, double-blind, well-controlled, prospective studies in the area of pharmacogenomics to clearly demonstrate the value of prospective genotyping in clinical practice. There are, however, considerable challenges in designing and financing such studies.

Abacavir, a guanosine reverse-transcriptase inhibitor and an important antiretroviral treatment against infection with the human immunodeficiency virus (HIV), has been used by almost 1 million patients infected with HIV during the past decade.⁵ In white populations, between 5 and 8% of patients receiving abacavir will have a serious hypersensitivity reaction characterized by fever, rash, and symptoms in the gastrointestinal tract, other organ systems, or both.

In 2002, a major discovery was that the HLA-B*5701 gene variant is highly associated with hypersensitivity reactions to abacavir.^{6,7} The identification of the HLA-B*5701 polymorphism was the result of microcytotoxicity studies and sequence analysis of the HLA-A, HLA-B, and HLA-C genes. These findings encouraged clinicians in Australia to carry out prospective HLA-B*5701 genotyping between 2002 and 2005, which led to a drastic reduction in the number of hypersensitivity reactions associated with abacavir,⁸ with no hypersensitivity reactions reported in 148 HLA-B*5701-negative patients. Similar results were later obtained in the United Kingdom and France. This relationship between HLA-B alleles and hypersensitivity reactions is less clear within black populations, for unknown reasons.⁹ Furthermore, in Asian populations, the frequency of HLA-B*5701 is very low, thus restricting the usefulness of this pharmacogenetic biomarker mainly to whites.

Molecular studies have revealed that abacavir is metabolized by class I alcohol dehydrogenase to form aldehydes and acids that covalently bind to cellular proteins and peptides.¹⁰ Initial studies showed that ex vivo stimulation of whole-blood specimens with abacavir leads to the release of tumor necrosis factor α and interferon- γ .¹¹ More recent work in progress suggests that abacavir triggers cytokine release from CD8+ T cells in blood in a response specifically involving

HLA-B*5701 and a proposed endogenous peptide.¹² These studies hold the promise of a more extensive understanding of the genetic and molecular basis of this reaction and the specific role the HLA-B*5701 polymorphism may play in abacavir-mediated hypersensitivity reactions. That role might explain the high selectivity of HLA-B*5701 as a pharmacogenomic biomarker.

In this issue of the *Journal*, Mallal et al.¹³ present the results of what has been strived for in the field of pharmacogenomics: a very large, randomized, double-blind, prospective study evaluating the clinical utility of a pharmacogenomic biomarker. Patients from 265 centers in 19 countries were randomly assigned to one of two treatment groups. One group of 847 patients received abacavir without prospective HLA-B*5701 screening; the other group of 803 patients received the drug only after prospective screening showed that they were negative for HLA-B*5701.

No immunologically confirmed hypersensitivity reactions were reported in patients who underwent prospective genotyping and were not carriers of HLA-B*5701; all hypersensitivity reactions occurred in carriers of HLA-B*5701. Approximately 50% of HLA-B*5701 carriers in the control group (2.7% of the patients who could be evaluated) who received abacavir had an immunologically confirmed hypersensitivity reaction. The relatively high incidence of no hypersensitivity reaction among HLA-B*5701 carriers might be explained by a reduced capacity to form the active peptide conjugate or mechanisms of immunologic tolerance that remain to be understood.

Is it appropriate to use HLA-B*5701 as a genetic biomarker in routine clinical practice? The answer, in my opinion, is yes. Only 14 patients would have to be screened to prevent one case of abacavir-induced hypersensitivity reaction. Such analyses have thus been shown to be cost-effective,¹⁴ and the data of Mallal et al. show that screening for HLA-B*5701 can reduce the incidence of hypersensitivity reaction to almost nil. Patients who carry HLA-B*5701 and who should receive abacavir, such as those requiring deep-salvage antiretroviral therapy, would be extremely rare because alternative medications are available. If abacavir therapy for such patients is unavoidable, however, careful monitoring for hypersensitivity reaction would be required for 6 weeks.

The drug industry is usually very hesitant to

release drugs requiring pharmacogenetic testing, because the basis for prescription is more complex than for drugs not requiring testing. However, the rate of prescription of abacavir has increased in the United Kingdom since prospective HLA-B*5701 genotyping was introduced (Pirmohamed M, University of Liverpool: personal communication). Thus, the use of validated pharmacogenetic biomarkers might result in increased, rather than decreased, use of medication and, in my opinion, the development of pharmacogenetic biomarkers may in many cases constitute an integral part of drug development.

HLA-B*5701 genotyping appears to be an effective pharmacogenomic test in white populations, with high sensitivity and modest specificity, allowing clinicians to avert a specific toxic effect of a drug. It is also an important precedent for further pharmacogenomic research toward safer, more effective individualized drug therapy.

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