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. 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. 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 In total, approximately 4% of all new medical agents are withdrawn from the market owing to adverse drug reactions. During the period 1995–2005, at least 34 drugs were withdrawn, mainly as a result of hepatotoxic or cardiotoxic effects — notably, cerivastatin, nefazodone, rofecoxib (Vioxx), terfenadine, and troglitazone.

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 clin-

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

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

* 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 identifica-
tion difficult. As a result, only a limited number 
of reports of a positive association between ge-
netic 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 prac-
tice. There are, however, considerable challenges 
in designing and financing such studies.

Abacavir, a guanosine reverse-transcriptase 
inhibitor and an important antiretroviral treat-
ment against infection with the human immuno-
deficiency 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 se-
rious 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 hy-
persensitivity reactions to abacavir.6,7 The identi-
fication of the HLA-B*5701 polymorphism was 
the result of microcytotoxicity studies and se-
quence 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 hyper-
sensitivity 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 with-
in black populations, for unknown reasons.9 Fur-
thermore, in Asian populations, the frequency of 
HLA-B*5701 is very low, thus restricting the use-
fulness of this pharmacogenetic biomarker main-
ly 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 abac-
avir triggers cytokine release from CD8+ T cells 
in blood in a response specifically involving 
HLA-B*5701 and a proposed endogenous pep-
tide.12 These studies hold the promise of a more 
extensive understanding of the genetic and mo-
lecular 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 pre-
sent the results of what has been strived for 
in the field of pharmacogenomics: a very large, 
randomized, double-blind, prospective study eval-
uating the clinical utility of a pharmacogenomic 
biomarker. Patients from 265 centers in 19 coun-
tries were randomly assigned to one of two treat-
ment groups. One group of 847 patients received 
abacavir without prospective HLA-B*5701 screen-
ing; 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 hypersensitiv-
ity reactions were reported in patients who under-
went prospective genotyping and were not carri-
ers of HLA-B*5701; all hypersensitivity reactions 
ocurred 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 immu-
nologically confirmed hypersensitivity reaction. 
The relatively high incidence of no hypersensitiv-
ity reaction among HLA-B*5701 carriers might 
be explained by a reduced capacity to form the 
active peptide conjugate or mechanisms of immu-
nologic tolerance that remain to be understood.

Is it appropriate to use HLA-B*5701 as a ge-
netic 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 ex-
tremely 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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