

The Pharmacogenomics Journal

EDITOR

Julio Licinio, UCLA, USA

EDITORIAL BOARD

J Azuma, Osaka University, Japan
E Boerwinkle, University of Texas, Houston, USA
U Brinkmann, Epidauros, Germany
RGH Cotton, University of Melbourne, Australia
D Flockhart, Georgetown University Medical Center, USA
P Froguel, Institut Pasteur de Lille, France
LM Furness, Incyte Genomics, UK
T Gingeras, Affymetrix, USA
M Hashida, Kyoto University, Japan
W Kalow, University of Toronto, Canada
T Klein, Stanford University, USA
I Kola, Pharmacia, USA
K Lindpaintner, Roche Genetics, Switzerland
R Long, National Institute of General Medical Sciences, USA
P Nadkarni, Yale University, USA
D Nickerson, University of Washington, USA
L Peltonen, University of California, Los Angeles, USA
M Polymeropoulos, Novartis, USA
G Poste, Health Technology Networks, USA
A Rane, Karolinska Institutet, Sweden
M Ratain, University of Chicago, USA
AD Roses, GlaxoSmithKline, USA
MA Rothstein, University of Louisville School of Medicine, USA
JC Venter, The Institute for Genomic Research, USA
R Weinshilboum, Mayo Clinic, USA
S Weiss, Harvard Medical School, USA
J Woodcock, Food and Drug Administration, USA
R Wolf, University of Dundee, UK
M-L Wong, University of California, Los Angeles, USA
A Wright, Western General Hospital, UK

EDITORIAL OFFICES

The Pharmacogenomics Journal
Nature Publishing Group
Specialist Journals Division,
Houndmills, Basingstoke,
Hampshire RG21 6XS, UK

and

The Pharmacogenomics Journal
Nature Publishing Group
Specialist Journals Division,
345 Park Avenue South
New York 10010-1707, USA

ThePharmacogenomicsJournal@nature.com
<http://www.nature.com/tpj>

Advances in the pharmacogenomics of adverse drug reactions

The Pharmacogenomics Journal (2002) 2, 273. doi:10.1038/sj.tpj.6500142

Adverse drug reactions (ADRs) are a gene-environment event that represents a major public health problem. In a meta-analysis of the literature, Lazarou *et al* found that in 1994, a total of 221 6000 (172 1000–271 1000) hospitalized patients in the U.S. had serious ADRs and 106 000 (76 000–137 000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death.¹ It is therefore crucial that research be directed at preventing such events. Pharmacogenomics offers the promise of ADR prediction. Urs Meyer proposes that three types of genetic mechanisms can influence the occurrence of ADRs. The first are polymorphisms of genes associated with the altered metabolism of drugs. Second, genetic variants can produce an unexpected drug effect. Third, genetic variation in a drug target can alter the clinical response and frequency of side effects.²

There is evidence supporting a role for pharmacogenomics in ADRs. Phillips *et al* showed that 27 drugs (including carbamazepine, fluoxetine, ibuprofen, isoniazid, naproxen, theophylline, phenytoin, verapamil and warfarin) are frequently cited in ADR studies. Of these 27 drugs, 59% are metabolized by at least one enzyme known to have allelic variants that cause poor metabolism. In contrast, only 7–22% of randomly selected drugs are known to be metabolized by enzymes with functional genetic variability.³ Even though ADRs represent an appealing target for pharmacogenomic studies, there are many limitations to such studies.⁴ These include the fact that relatively small numbers of patients have ADRs compared to the total number of patients who are treated with a drug, making clinical follow-up of large numbers of subjects a costly necessity. Additionally, complex comparisons between affected and nonaffected individuals exposed to a drug are needed, with a large number of genotypes at various loci required.

Such potential limitations did not discourage Acuña *et al*, who report in this issue (pages 327–334) the use of a pharmacogenomic strategy to predict liver toxicity due to tolcapone, a catechol-*O*-methyltransferase (COMT) inhibitor used in the treatment of Parkinson's disease. Owing to hepatotoxicity, this drug has been taken off the market in some countries (such as the United Kingdom) and is available in others (such as the United States) with warnings. Using a case-control study design, 135 patients taking tolcapone who had levels of liver transaminase at least 1.5 times above normal were matched with 274 controls who took the same drug, but did not suffer from liver toxicity. In all, 12 candidate genes involved in the known metabolic pathways of elimination of this drug were chosen as targets for analysis. Because glucuronidation is the main pathway for tolcapone elimination, the authors conducted SNP identification studies of the UDP-glucuronoyl transferase 1 (UGT1) gene complex and found six new single nucleotide polymorphisms (SNPs). Using a combination of known and new SNPs, the authors showed a significant association between the phenotype of hepatotoxicity and genotype, with the power of marker genotypes being sufficient to allow accurate prediction in 61% of elevated liver transaminase cases. These interesting results show that pharmacogenomics research can (1) contribute to further characterize clinically relevant variation in the human genome and (2) predict ADRs. As usual, issues of replication in other samples and additional population groups who may have different allele frequencies must be addressed before the wide applicability of these results can be determined. Nevertheless, the elegant study design and interesting results obtained by Acuña *et al* provide justification for cautious optimism regarding the translation of pharmacogenomics research into clinical practice.

REFERENCES

- 1 Lazarou J, Pomeranz B, Corey P. *JAMA* 1998; **279**: 1200–1205.
- 2 Meyer UA. *Lancet* 2000; **356**: 1667–1671.
- 3 Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. *JAMA* 2001; **286**: 2270–2279.
- 4 Roden DM, George Jr AL. *Nat Rev Drug Discov* 2001; **1**: 37–44.

I Alvarado, M-L Wong and J Licinio
UCLA Laboratory for Pharmacogenomics, CA, USA