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Advances in the pharmacogenomics of adverse drug reactions

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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, teophylline, 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.

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