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## **Pharmacogenetics of adverse drug reactions**

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### **Introduction**

Pharmacogenetics and pharmacogenomics are two terms often used interchangeably to describe the study of the genetic basis for inter-individual differences in response to drugs. The aim of pharmacogenetics therefore is to identify genetic factors leading to adverse drug reactions (ADRs) and through this develop predictive genetic tests to reduce (but possibly not abolish) the harms associated with medicines.

There is no doubt that ADRs are a major clinical problem. A prospective study conducted in the UK demonstrated that about 6.5% of hospital admissions were ADR-related [1]. ADRs not only prolong hospital stay, but can also occur after admission in almost 20% of patients [2]. However, how many of these will be preventable through genetic prediction?

Studies have shown that the occurrence of ADRs is due to many factors including both environmental and genetic factors. The former category represents a collection of causes ranging from poor compliance to poor prescribing. Indeed, it has been suggested that almost two-thirds of ADR-related hospital admissions may be preventable through better medical and prescribing practice [3]. From this, it can be argued that genetics is therefore only going to be important in one-third of all ADRs. However, this may represent an under-estimate because many of the drugs involved in ADRs due to poor prescribing practice have a narrow therapeutic index, where the margin between safety and hazard is very narrow. A typical here is warfarin where there is a 20-fold variation in dose requirements, and both under- and over-anticoagulation are associated with potentially lethal adverse effects. At least two genetic factors (CYP2C9 and VKORC1) determine, at least partially, maintenance dose requirements. By incorporating these genetic factors into the prescribing practice for warfarin, it may be possible to effectively widen the therapeutic index, and thereby reduce the potential problems associated with poor prescribing practice. In view of this,

we cannot at present state with any confidence the overall contribution that genetic factors play in the predisposition to ADRs.

The essential aim therefore should be to identify genetic factors associated with ADRs with all drugs, and effectively incorporate pharmacogenetics into the practice of pharmacovigilance. Clearly, according to current definitions, the role of pharmacovigilance is to detect and assess risks of ADRs prior to and during the marketing of medicines, to evaluate drugs in clinical use, to implement measures for reducing risks and to monitor the effectiveness of risk minimising interventions. The science of pharmacogenetics is perfectly consistent with this definition because it allows the detection and prediction of ADRs, and is a tool that can reduce the risks associated with ADRs.

### **Clinical impact of pharmacogenetics**

Genetic susceptibility to ADRs has been established for a number of drugs. Recently, for example, strong genetic associations in the major histocompatibility complex on chromosome 6 with ADRs to carbamazepine (an antiepileptic drug), abacavir and nevirapine (both antiretrovirals) and allopurinol, a drug used to treat gout [4, 5]. The genetic association between abacavir hypersensitivity and HLA-B\*5701 has actually been translated into clinical practice – recent data from Australia and the UK have shown that pre-prescription genotyping leads to a clinically significant reduction in the frequency of abacavir hypersensitivity. Moreover, it has been shown that pre-prescription genotyping for abacavir hypersensitivity is a cost-effective strategy.

However, overall the clinical impact of pharmacogenetics has been relatively poor, apart from the small number of tests listed in Table 1, which can be regarded as being in use in some but not all clinics.

Table 1. Pre-treatment genetic testing already available in clinical practice.

| <b>Drug Examples</b>              | <b>Adverse drug reaction</b> | <b>Implicated Gene/allele</b>     |
|-----------------------------------|------------------------------|-----------------------------------|
| Azathioprine and 6-mercaptopurine | Haematologic toxicity        | Thiopurine S-methyltransferase    |
| Abacavir                          | Hypersensitivity reaction    | HLA-B*5701                        |
| Primaquine                        | Haemolytic anaemia           | Glucose-6-phosphate dehydrogenase |
| Irinotecan                        | Diarrhoea and leukopenia     | UDP-glucuronyltransferase 1A1     |

There are several possible reasons as to why pharmacogenetics has had little impact on clinical practice. First, many studies that have evaluated genetic predisposition to ADRs have been small-scale studies, often under-powered to detect small genetic effect sizes. This is to some extent understandable given the rarity of such reactions and the difficulty in identifying patients and collecting samples. In most cases, case-control study designs have been used. Although this may be appropriate for the rare adverse events, alternative study designs, for example cohort studies, which allow better evaluation of environmental factors have to be considered, particularly when the adverse reaction is relatively more common in the population.

Second, the clinical phenotype is often poorly defined with pooling of patients with different types of adverse reactions. Clearly, the clinical picture of ADRs

caused by the same drug can vary widely in severity and manifestations in different individuals (Table 2).

Table 2. Genetic association of carbamazepine hypersensitivity in two populations, Han Chinese and Caucasians.

| Clinical manifestation    | Genetic associations |                                   |
|---------------------------|----------------------|-----------------------------------|
|                           | Han Chinese          | Caucasian                         |
| Maculopapular rash        | HLA-E, HLA-A*3101    | Not identified                    |
| Hypersensitivity syndrome | MLN‡                 | TNF-308, HLA-DR3, HLA-DQ2, HSPA1L |
| SJS/TEN                   | HLA-B*1502           | Not identified                    |

Clinical manifestations are of variable severity - the mildest form is an isolated maculopapular skin rash. Hypersensitivity syndrome comprises skin rash accompanied by systemic symptoms, including fever, eosinophilia and hepatitis. Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are blistering skin rashes and have up to a 30 % fatality rate.

‡ MLN, motilin located on chromosome 6p21.3, a 22-amino acid hormone synthesized by cells of the small intestine, regulates interdigestive gastrointestinal contraction.

An example here is cutaneous toxicity: a maculopapular eruption may not necessarily have the same genetic predisposition as hypersensitivity syndrome or the blistering skin diseases, and if possible, these reactions should be analysed separately. It is therefore likely that the diversity in phenotype represents one of the most important reasons for non-replication of a pharmacogenetic association found to be positive in an initial study. Indeed, this is consistent with the fact that stronger genetic effects are often seen in the first study than in any subsequent studies of the same association [6]. A possible solution may be the use of intermediate phenotypes or “endophenotypes”, which are quantifiable traits predictive of a clinical phenotype. These may provide a more accurate and reproducible measure of adverse drug responses.

Third, pharmacogenetics is a study of the pharmacology of the drug in relation to genetic variation. Thus, the pharmacological phenotype is extremely important, but this is often poorly defined. The effect of a pharmacologically active substance is dependent on its concentration at its site of action. The final concentration will depend not only on genetic factors but also on environmental factors, adherence to the medication and constitution of the formulation. Where possible, note should be taken of these factors to improve the phenotype of drug response.

Fourth, inadequate genotyping strategies have been adopted in the past because of our lack of knowledge and the high genotyping costs. Thus, most pharmacogenetic studies have pursued the concept of single gene, single variants affecting drug response. This is clearly simplistic, and given that we now have the technologies that are readily available and relatively cheap to use, we need to assess the genetic diversity of the whole gene. This is happening through the analysis of multiple SNPs and haplotypes in multiple genes covering the whole pathway of drug action. As the costs of genotyping decrease further, we also have the possibility of undertaking unbiased whole genome scans. This is an exciting possibility, which is likely to lead to the identification of novel

predisposing factors for adverse drug reactions, but does require the collection of large numbers of patients to ensure adequate statistical power.

#### Large population studies on adverse drug reactions

As serious ADRs are rare, international collaboration is needed to collect large numbers of patients to ensure that studies are adequately powered to detect small genetic effects. An example of this is the EUDRAGENE project [7] which aims to establish a case-control collection of DNA samples for studying genetic factors of various ADRs (Table 3).

Table 3. The initial selection of adverse reactions to be studied in the EUDRAGENE project.

| <b>Adverse drug reaction</b> | <b>Drugs and drug classes</b>                     | <b>Number of ADRs reported for a 5-year period in 9 EU countries*</b> | <b>Prevalence (reported ADRs/total population)</b> |
|------------------------------|---|---|--|
| Torsades de pointes          | Anti-arrhythmics<br>Antibiotics<br>Antipsychotics | 327   | 1/million  |
| Long Q-T syndrome            | Same as above                                     | 228   | 0.7/ million                                       |
| Myopathy                     | Statins<br>Fibrates                               | 3143  | 9/million  |
| Rhabdomyolysis               | Statins<br>Fibrates                               | 593   | 1.7/million  |
| Agranulocytosis              | Thyroid inhibitors<br>Sulphasalazine<br>Clozapine | 2796 total  | 8/million  |
| Liver injury‡                | NSAIDS  | 1758  | 5/million  |
| Tendinitis/tendon rupture    | Fluoroquinolones                                  | 1993  | 6/million  |
| Psychosis                    | Mefloquine  | 1516  | 4/million  |

\*EU countries involved in EUDRAGENE project: Italy, Sweden, Germany, Belgium, Spain, France, Netherlands, Norway and UK (total population estimated to 345 millions).

‡ All drug classes that cause hepatotoxicity will be studied in EUDRAGENE. Taken from Molokhia and McKeigue [7].

More recently, the Serious Adverse Event Consortium has also been set up under the aegis of the FDA, and represents collaboration between industry, regulators and academia to collect patients with severe adverse reactions, for example those affecting the liver, and then undertake whole genome scanning to identify novel genetic determinants. There are likely to be further examples of this approach in the near future. However, these collections utilise a case-control methodology, and we also need to be planning for the long-term through the development of well phenotyped cohorts of patients where database information is linked, with appropriate ethical and regulatory oversight, to biobanks comprising DNA, serum and urine samples. This will allow investigators to investigate static (DNA) and dynamic markers (such as protein and metabolites). The UK Biobank is an example of such an approach, but is not targeted at evaluating factors determining drug response, but more towards genetic determinants of disease.

### Adding pharmacogenetic information to drug labels

One of the most important factors that will lead to the use of pharmacogenetic tests in clinical practice will be regulatory action that changes the drug label. The best example of this is with trastuzumab (Herceptin), which is used in patients with HER2-positive breast cancer. Pharmacogenetic information has been added to a number of other drug labels including azathioprine, atomoxetine, irinotecan and tamoxifen by the FDA. However, in every instance, the label does not mandate testing, but is for information only. This may reflect the lack of accurate data on clinical utility for most of these pharmacogenetic associations. It is also not clear what level of evidence is going to be needed by regulators to change a label from one that is informative to one that is mandatory, but is likely to vary with the individual drugs. A label change is also being proposed for warfarin by the FDA. This is likely to contain information on the relationship of warfarin dose requirements with the CYP2C9 and VKORC1 gene polymorphisms. Although dosing algorithms based on these genetic predictors have been developed for warfarin, it is unclear whether these will be recommended in the label. Perhaps this reflects the fact that the majority of studies on warfarin to date have been retrospective, have had different inclusion criteria, and may have limited external validity. In order to improve the evidence base for warfarin, we are currently undertaking a multi-centre prospective study on the genetic and environmental factors that determine warfarin dose requirements and liability to adverse effects (Figure 1). This will provide (a) better data on genetic and environmental contributions to variability with warfarin, and (b) a framework for the design of a randomised controlled trial, which assesses the clinical utility and validity of genotype-guided prescribing.

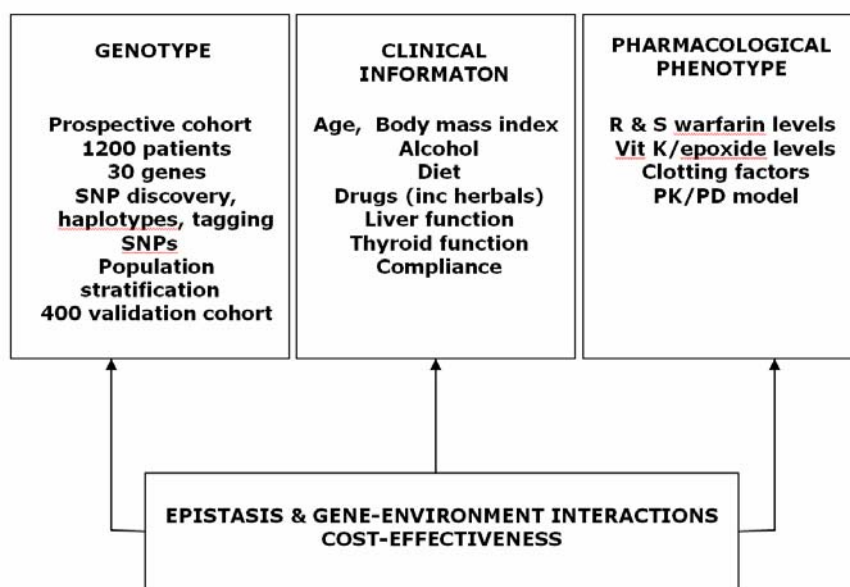


Figure 1. An example of a prospective study designed to assess the genetic and environmental factors determining the dose requirements for the anticoagulant drug warfarin. Genetic information includes determination of polymorphic variants in 30 genes, and haplotype analysis based on haplotype tagging SNPs. To make sure that positive associations are not due to undetected population stratification, genetic population markers will be determined. In addition to the genotype, accurate clinical and pharmacological phenotypes will be ascertained. It will be possible to assess gene-gene, and gene-environment interactions, as well as to determine the cost-effectiveness of testing. (PK/PD = pharmacokinetic/pharmacodynamic)

### Conclusions

ADRs have a multigenic and multifactorial aetiology, akin to that observed with complex diseases. Genetic factors may play a major role in the pathogenesis of many adverse drug reactions, and pre-prescription testing may allow us to prevent or at least minimise the harms associated with these adverse effects, as has been shown for abacavir hypersensitivity. However, demonstration of the clinical utility of these tests is going to be crucial before they can be recommended for use in clinical practice. Large multi-centre studies are urgently needed to identify and collect samples from well phenotyped patients with ADRs, which will serve as a resource to establish individual susceptibility to the ADRs. With the advances in technologies (genotyping, proteomic, metabonomic, informatics and statistical), pharmacogenetics, in the wider context of a systems biology approach has the potential to help in predicting the toxicity of drugs and through this bring us closer to the concept of personalised medicines, whereby every patient is prescribed the right drug at the right dose to maximise benefit and minimise harm.

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