Pharmacogenetics – p

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Current and future developments in pharmacogenetics and pharmacogenomics have often been cited in the scientific literature to be the path towards personalized prescribing, allowing for individualized optimization of therapeutic efficacy and minimization of adverse drug reactions. Further research coupled with the establishment of sound ethical guidelines may soon allow pharmacogenetic DNA testing to become part and parcel of standard clinical practice.

Introduction

The term 'pharmacogenetics' first appeared in the scientific literature in 1959.[1] It was coined by Friedrich Vogel, and he used it to refer to the influence of genetic factors on the response to drugs. The existence of inter-patient variability to drug responses had long been recognised for several years, but it is only recently with the help of advances in molecular genetics, that science has began to unravel the secrets within our genome that may contribute to this variability.

Pharmacogenetics or pharmacogenomics?

The advent of large scale, high throughput molecular research, has brought with it new terminology. While the meaning Vogel assigned to 'pharmacogenetics' has been traditionally maintained, a newer term, 'pharmacogenomics', is used to describe the study of whole genomes, or large numbers of genes relevant to drug response at a cellular, tissue, individual or population level. Such pharmacogenomic approaches have a role in the identification of novel putative drug targets, and in the study of the influence of drugs on the expression of a large number of genes.[2,3]

Pharmacogenetic variation

There is a rapidly growing list of genetic polymorphisms which are being recognised to influence drug responses. Such variations have been identified in both coding and regulatory regions for genes which encode drug metabolizing enzymes, receptor proteins, drug transporter molecules as well as other proteins which are involved in the pharmacological pathway of the drug in question.[4] Some examples will be treated below.

Mercaptopurine is predominantly inactivated by the enzyme thiopurine S-methyl transferase (TPMT). About 10% of the population is heterozygous for the TPMT gene, and carry an allelic variant that is incapable of producing functional TPMT enzyme, while 0.3% is homozygous for the mutant alleles and are not capable of producing any functional enzyme. Patients with low TPMP activity and who are treated with mercaptopurine accumulate excessive concentrations of active thioguanine molecules in blood cells, leading to potentially severe haematopoietic toxicity. Indeed, homozygous mutant individuals only require 5-10% of the conventional doses for successful treatment.[5,6] CYP2D6, a member of the Cytochrome P450 family, is responsible for the metabolism of several pharmacologically unrelated drugs, including antidepressants, codeine and beta-blockers, while CYP2C9 is responsible for the metabolism of NSAIDs, warfarin, tolbutamide and phenytoin. Functional variants of the genes for these enzymes, which result in the production of altered enzymatic activity have been identified. Patients inheriting these variants, show altered pharmacokinetic profiles to these drugs, resulting in either potentially toxic blood levels or low blood concentrations of the active drug which would be conducive to decreased therapeutic efficacy.[7,8,9]

Gene promoter variants may potentially influence the rate of transcription of a particular gene, and therefore the level of expression of the protein product. Specific polymorphic variation within the promoter regions of the gene coding for the 5-lipoxygenase enzyme (ALOX) has been associated with non-response to zafirlukast, a cysteinyl leukotriene-receptor antagonist drug used in the management of bronchial asthma. Asthmatic patients carrying this ALOX promoter variant, would therefore not benefit from this drug.[10,11]

Beta-2 adrenoceptors are G-protein coupled receptors which are primarily expressed on airway smooth muscle cells and constitute the target for beta-2 agonist bronchodilator drugs such as salbutamol, terbutaline, formoterol and salmeterol. Nine single nucleotide polymorphisms have been identified in the beta-2 adrenoceptor coding region, of which 4 result in amino acid substitutions at the protein level. Two of these have been shown to be functionally relevant. One variant, for which the sixteenth amino acid is glycine instead of arginine (Arg16–>Gly), has been shown to downregulate faster in the presence of agonists,[12] and indeed patients who are homozygous for Gly16 have been shown to develop tachphylaxis to formoterol treatment faster than patients who carry the Arg16 variant.[13] A second polymorphism (Gln27–>Glu) confers on the receptor a strong *resistance* towards agonist-promoted desensitization and downregulation.[14] The results of this effect have been observed both *in vitro* as well as *in vivo*.[15]

Personalized patient prescribing

The aim of pharmacogenetic research is to eventually develop DNA testing procedures that will enable a prescriber to predict a patient's response to a particular drug in terms of efficacy as well as predict the potential for development of particular severe adverse drug reactions. This approach aims to select the right medicine for the right patient, and would be expected to revolutionise treatment outcomes with positive impacts on health quality and costs.[16,17] The development and eventual commercial availability of 'bedside' pharmacogenetic tests introduces a hitherto undetermined new cost-factor into the pharmacoeconomic picture. This should not adversely tip the scales of the cost-benefit ratio.

It might eventually become relevant to pharmacogenetically stratify volunteers participating in clinical trials, in order to gain a better understanding and assessment of drug efficacy in specific genetically defined patient populations. Pharmaceutical companies may be provided with a niche market, for the development of new drugs for specific use in patients who are

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pharmacogenetically compromised with respect to currently available therapy. However financial viability remains a variable in this equation.

Ethical issues

The future availability of pharmacogenetic testing for specific drugs is not devoid of ethical dilemmas. A pharmacogenetic test might reveal more knowledge than is specifically intended. For example, a patient who is a rapid metabolizer for a particular drug, is likely to also rapidly metabolize other pharmacologically unrelated drugs which share the same metabolic pathways. Should such additional information be disclosed to the patient? In the clinical setting, a patient might be expected to provide informed consent for a pharmacogenetic test to be carried out. The implications of such a test should be clearly explained, and the result should be accompanied by professional advice. Ethnicity may bear an influence on the validity of a pharmacogenetic test, since specific genotypes may only be present in particular populations. Will test developers take this into account, or will particular populations be sidelined due to marketing or financial considerations? It is possible that pharmacogenetic information may be requested by insurance companies, to aid in the computation of health insurance premiums, thus potentially dissuading patients from consenting to such tests for fear of having to pay higher premiums or being unable to obtain insurance. It is applaudable that the UK imposed a moratorium on the use of genetic and pharmacogenetic data for setting insurance premiums. This moratorium however expired in 2006.[2,18]

Conclusion

Although rapidly expanding, it is debatable whether the current status of available pharmacogenetic data is sufficient to justify routine genotyping of all patients prior to initiation of any specific pharmacological treatment. However, as new genetic data becomes available, and novel therapies are developed, the knowledge of patients' genotypes will be a necessary requisite in order to enable pharmaceutical companies and prescribers to optimize management of a disease. Further clinical and molecular work is needed in order to consolidate and expand current knowledge, and a search of the scientific literature databases will show that such work is rapidly advancing forward. The present status suggests that pharmacogenetic testing for specific drugs may be available sooner rather than later.[19,20] The importance of this area of research has been accented by the recent UK Department of Health announcement of a commitment of £4 million over 3 years to be granted to pharmacogenetic research.[2]

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