Pharmacogenomics: marshalling the human genome to individualise drug therapy

W E Evans

Pharmacogenomics aims to identify the inherited basis for interindividual differences in drug response, and translate this to molecular diagnostics that can be used to individualise drug therapy. This review uses a number of published examples of inherited differences in drug metabolising enzymes, drug transporters, and drug targets (for example, receptors) to illustrate the potential importance of inheritance in determining the efficacy and toxicity of medications in humans. It seems that this field is at the early stages of developing a powerful set of molecular diagnostics that will have profound utility in optimising drug therapy for individual patients.

Pharmacogenomics is a rapidly emerging field that aims to elucidate the genetic basis for interindividual differences in drug response, using genome wide approaches to identify genetic polymorphisms that govern an individual’s response to specific drugs.1–4 As described in the initial reports from the human genome project,1 there are over 1.4 million single nucleotide polymorphisms (SNPs) in the human genome, with over 60 000 of these residing in the coding region of human genes, and the number of SNPs will grow as more humans are studied. Some of these SNPs have already been associated with significant changes in the metabolism or effects of commonly used drugs and are beginning to make their way into clinical medicine as molecular diagnostics.4 For some genetic polymorphisms (for example, thiopurine S-methyltransferase (TPMT), cytochrome P4502D6), monogenic traits have a marked effect on drug disposition (for example, pharmacokinetic changes attributable to aberrant drug metabolism), and people who inherit the enzyme deficiency must be treated with substantially different doses of some affected drugs (for example, 5%–10% of the standard mercaptopurine or azathioprine dose in patients inheriting two mutant TPMT alleles).5–8 Likewise, polymorphisms in drug targets (for example, β adrenoceptor, 5-lipoxygenase) have been shown to change the sensitivity of patients to treatment with medications that interact with these targets (for example, β agonists, zileuton), changing the pharmacodynamics of drug response.5–8 Because most drug effects are determined by the interplay of several gene products that govern the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics is increasingly focused on elucidating polygenic determinants of drug effects (fig 1).

The potential importance of pharmacogenetics has been recognised for many years; clinical observations of inherited differences in drug effects were first reported in the 1950s11–14 giving rise to the field of “pharmacogenetics”, which has now been embraced by a broader spectrum of academia and industry, giving birth to “pharmacogenomics”. The two terms are commonly used interchangeably to describe genetic determinants of drug disposition and response. There are now numerous examples establishing that interindividual differences can be attributed, at least in part, to polymorphisms in genes encoding drug metabolising enzymes, drug transporters and/or drug targets (for example, receptors, enzymes).1–4 While it is clear that many non-genetic factors influence the effects of medications, including a person’s age, race, sex, organ function, concomitant therapy, disease severity, and drug interactions, inherited determinants of drug disposition and effects remain stable for a person’s lifetime and can have marked effects, independent of the non-genetic factors.

The human genes involved in many pharmacogenetic traits have now been isolated, their molecular mechanisms elucidated, and their clinical importance more clearly defined (reviewed in references1–4). This review provides a number of examples of genetic polymorphisms that determine a person’s response to drugs, and how this can be translated to clinical practice via molecular diagnostics (genotyping) to guide the selection of medications and drug doses that are optimal for the individual patient.

POLYMORPHISMS IN GENES INFLUENCING DRUG DISPOSITION

While pharmacogenetics began with a focus on drug metabolism, it has now been extended to all aspects of drug disposition, including a growing list of drug transporters that influence drug absorption, distribution, and excretion (table 1).1–4

Drug metabolising enzymes

There are over 30 families of drug metabolising enzymes in humans,1 and essentially all have genetic variants, many of which cause functional changes in the proteins encoded, and thereby change the metabolism of drugs.

Thiopurine methyltransferase (TPMT) and azathioprine, mercaptopurine, or thioguanine therapy

The genetic polymorphism of TPMT is one of the most well developed examples of clinical pharmacogenomics. TPMT catalyses the S-methylation of...
the thiopurine agents azathioprine, mercaptopurine and thioguanine. These agents are commonly used for a diverse range of medical indications, including leukaemia, rheumatic diseases, inflammatory bowel disease, and solid organ transplantation. The principal cytotoxic mechanism of these agents is generally considered to be mediated via the incorporation of thioguanine nucleotides (TGN) into DNA. Thus, thiopurines are inactive prodrugs that require metabolism to TGN to exert cytotoxicity. This activation is catalysed by a multi-enzyme pathway, the first of which is hypoxanthine phosphoribosyltransferase (HPRT). Alternatively, these agents can be inactivated via oxidation by xanthine oxidase or methylation by TPMT. In haematopoietic tissues, xanthine oxidase is negligible, leaving TPMT as the only inactivation pathway. In a study of azathioprine for rheumatic disease, patients with wild type TPMT received treatment for a median 39 weeks without complications compared with a median of two weeks in patients heterozygous for one mutant TPMT allele and one wild type allele. A second study in Japanese rheumatic disease patients receiving azathioprine recently confirmed the importance of a heterozygous TPMT genotype for predicting systemic toxicity. A more quantitative analysis of mercaptopurine for childhood ALL found that TPMT deficient patients tolerated full doses of mercaptopurine for only 7% of weeks, whereas heterozygous and homozgyous wild type patients tolerated full doses for 65% and 84% of scheduled weeks of treatment over the 2.5 years of treatment, respectively. The percentage of weeks in which mercaptopurine dose had to be decreased to prevent toxicity was 2%, 16%, and 76% in wild type, heterozygous, and homozygous mutant individuals. Collectively, the above studies show that the influence of TPMT genotype on haematopoietic toxicity is most dramatic for homozygous mutant patients, but is also of clinical relevance for heterozygous individuals, which represent about 10% of patients treated with these drugs.

Prospective determination of functional TPMT status is of clinical utility to prevent mercaptopurine and azathioprine...
Examples of genetic polymorphisms of human drug metabolising enzymes and transporters

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Genetic polymorphisms do not always translate into distinct phenotypic differences in drug metabolism in population studies, exemplified by a common polymorphism in the P450 enzyme CYP3A5. The CYP3A5 protein is expressed in only about half of African-Americans and about 20% of the white population, and those people who express both CYP3A5 and CYP3A4 have higher total CYP3A enzyme activity, which translates to higher rates of drug clearance when medications are metabolised by both enzymes. Moreover, gene duplication of CYP2D6 leads to inheritance of an “ultrarapid metaboliser” phenotype, which has been linked to treatment failure for some antidepressant and antipsychotic drugs.

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Glutathione S-transferases
Glutathione is conjugated to many electrophiles, including several medications and their potentially damaging oxidative toxicity. TPMT genotyping is now available as a molecular diagnostic from reference laboratories, representing the first CLIA certified pharmacogenetics test for individualising drug treatment based on a patient’s genotype. Patients with a “low methylator” status (homzygous mutant or compound heterozygote) may tolerate standard doses, but are at significantly greater risk of toxicity, often necessitating a lower dose of these drugs (50%–80% of standard doses).

Cytochrome P450 enzymes
The cytochrome P450 enzymes represent a large family of drug metabolising enzymes, catalysing the metabolism of more medications than any other family of enzymes. Debrisoquin hydroxylase (CYP2D6) is probably the most well characterised genetic polymorphism in cytochrome P450 enzymes, representing the first human polymorphic drug metabolising enzyme to be cloned and characterised at the molecular level. As was common in the pre-genomics era, its discovery was in part serendipitous, facilitated by the principal investigator’s development of marked hypotension during participation in a pharmacokinetic study of debrisoquine, an antihypertensive.

Family studies subsequently showed that he had inherited a deficiency in debrisoquin metabolism, an enzyme deficiency discovered independently with sparteine.

Many drugs (>30) were subsequently found to be substrates for CYP2D6, and this genetic polymorphism was documented in most populations worldwide, with pronounced racial differences in mutant allele frequencies. A large number of CYP2D6 SNPs, gene deletions and gene duplications have now been discovered, and concordance between genotype and phenotype has been well established for many drug substrates.

CYP2D6 deficiency can result in either exaggerated drug effects when CYP2D6 is the major inactivation pathway (for example, tricyclic antidepressants, fluoxetine) or diminished effects when CYP2D6 is required for activation (for example, codeine). Moreover, gene duplication of CYP2D6 leads to inheritance of an “ultrarapid metaboliser” phenotype, which has been linked to treatment failure for some antidepressant and antipsychotic drugs.

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Discovery of the genetic basis for CYP3A5 deficiency makes it possible to easily identify those patients who express CYP3A5 based on their genotype, but the clinical importance of these CYP3A genetic polymorphisms has not been fully elucidated to date.
metabolites. Conjugation with glutathione generally inactivates these reactive moieties, although this is not always the case. These conjugation reactions are catalysed by a family of human glutathione S-transferases (GST), and the human genes encoding these enzymes are highly polymorphic, with about 50% and 25% of most populations having a complete deletion of GST-M1 and GST-T1, respectively, rendering them void of these enzyme activities. As is typical for many gene polymorphisms, there are important racial and ethnic differences in the frequencies of gene deletions in different human populations. Other GSTs, that is, GST-P1 and GST-A1, are also subject to genetic polymorphisms, and these have been implicated in resistance to several anti-cancer agents.

Several studies have reported associations between GST polymorphisms and the efficacy and/or toxicity of cancer chemotherapy. High GST activity has been associated with resistance to anticancer agents, consistent with the association of inherited GST deficiencies with a decreased risk of haematological relapse and central nervous system relapse, and to improved prednisone response in children treated with combination chemotherapy for acute lymphoblastic leukaemia. Similarly, inheriting a GST-P1 allele coding for the IleVal amino acid substitution has been associated with improved overall breast cancer survival, compared with patients who had at least one wild type allele.

In breast cancer patients, deletion of either GST-M1 or GST-T1 was associated with improved survival, with further improvement in outcome if both genes were deleted. In contrast, in patients with acute myeloid leukaemia treated with high doses of combination chemotherapy, the homozygous GST-T1 deletion was associated with a higher risk of toxic death during remission, most probably because such patients could not tolerate intensive chemotherapy due to the absence of detoxifying GST enzymes. Together, these studies in breast cancer and AML patients illustrate that the importance of a genetic polymorphism in drug metabolism may differ based on the nature and intensity of the treatment regimen being prescribed. When treatment intensity is comparatively modest, leading to potential under treatment of some patients, then inheriting an enzyme deficiency can increase the exposure to drugs that are substrates, and thereby increase their efficacy. Conversely, when drugs are being dosed at levels that are near those that produce toxicity (common in AML), then inheritance of an enzyme deficiency can lead to a worse outcome because of greater toxicity.

### Drug transport proteins

Transport proteins play an important part in human physiology and pharmacology, providing protective functions (for example, blood-brain barrier), contributing to critical cellular processes (for example, biliary excretion), and influencing the absorption of drugs and other compounds from the small intestine. The ATP binding cassette (ABC) family of membrane transporters, comprise an extensively studied group of transporters influencing drug disposition and effects. P-glycoprotein (PGP), a member of the ABC family, is involved in the energy dependent efflux of substrates, including bilirubin, several anticancer drugs, cardiac glycosides, immunosuppressive agents, glucocorticoids, HIV-1 protease inhibitors, and many other drugs. Expression of the PGP gene (ABCB1, also names MDR1) in normal tissue suggests that it is involved in excreting drugs and their metabolites into urine, bile, and the intestinal lumen. At the blood-brain barrier, PGP in the choroid plexus limits brain accumulation of many drugs, including cyclosporin A, dexamethasone, digoxin, domperidone, loperamide, and vinblastine (table 2).

PGP expression differs markedly among individuals, the molecular basis of which has not been fully elucidated. Recently, a synonymous SNP in exon 26 (3435C>T), was reported to be associated with duodenal PGP protein expression; patients homozygous for the T allele had more than twofold lower duodenal PGP expression compared with patients with CC genotypes. Clinical pharmacokinetic studies of digoxin, a PGP substrate, demonstrated significantly higher bioavailability in patients with the CC genotype. As is common for most genetic traits, there are considerable ethnic differences in the frequency of the 3435C>T SNP; the TT genotype was found in 0%–6% of black African and African-Americans, 20–47% of Asians, and 24–36% of the white population. However, the 3435C>T SNP is in linkage disequilibrium with a non-synonymous SNP in exon 21 (1236C>T, Ala893Ser) that has been shown to change PGP function, so it is unclear whether the 3435C>T SNP is of functional importance or just in linkage with the functionally important SNP in ABCB1.
tiation of antiretroviral treatment, suggesting a potential strategy to individualise HIV therapy, if these findings can be independently verified.

GENETIC POLYMORPHISM OF DRUG RECEPTORS AND OTHER TARGETS

Genetic variation in drug targets (for example, receptors) can have a profound effect on drug effects, with over 25 examples already identified, including the β2 adrenoceptor and response to β2 agonists,5-6 angiotensin converting enzyme and renoprotective effects of ACE inhibitors,7 apolipoprotein E and response to HMG-CoA reductase inhibitors (“statins”)8 and more than 20 other examples (reviewed in references 1–3). The potential importance of these genetic polymorphisms is exemplified in this review by the β2 adrenoceptor.

Genetic polymorphism of the β2 adrenoceptor exemplifies a well characterised and clinically relevant polymorphism in a drug target.4 The β2 adrenoceptor is a G protein coupled receptor that interacts with various medications and endogenous catecholamines. These receptors are widely expressed in humans and play an important part in regulating cardiac, vascular, pulmonary, and metabolic functions.4-6 Studies of such physiological functions of the human β2 adrenoceptor have revealed substantial interpatient differences in receptor function and responsiveness to stimulation. In the heart, activation of the β2 adrenoceptor results in an increased rate and force of cardiac muscle, whereas β2 adrenoceptor stimulation in the lungs acts to relax airway smooth muscle. Effects on lipolysis in subcutaneous fat have also been reported, mediated putatively through regulation of lipid mobilisation, energy expenditure, and glycogenolysis. Insights to the molecular basis for inherited differences in the β2 adrenoceptor have been illuminated by the discovery of several SNPs in the B2AR gene, and their association with altered expression, down regulation, or coupling of the receptor.6 Single nucleotide polymorphisms resulting in an Arg to Gly amino acid change at codon 16 and a Gln to Glu change at codon 27 are comparatively common (allele frequency = 0.4–0.65) and are being extensively investigated for their clinical importance. Studies of agonist mediated vasodilatation and desensitisation have begun to dissect the relative contribution of the codon 16 and codon 27 mutations.5 Subjects who were homozygous for Arg16 had nearly complete desensitisation after continuous infusion of isoproterenol, with venodilatation decreasing from 44% at baseline to 8% at 90 minutes. Homozygous Gly16 patients had no significant change in venodilatation, regardless of their codon 27 sequence. Polymorphism at codon 27 was also of functional relevance, as patients homozygous for Glu27 had higher maximal venodilatation in response to isoproterenol (86%) than observed in subjects with the codon 27 Gln genotype, regardless of codon 16 sequence.6

These results are consistent with the reported effects of B2AR genotype on pulmonary response to acute or chronic β2 agonist therapy. The FEV1 response to a single dose of oral albuterol was more that sixfold higher in patients with an Arg/Arg genotype at codon 16 compared with Gly/Gly patients, even though similar plasma drug concentrations were achieved.8 Interestingly, the influence of this genotype changed when long term inhaled β2 agonist therapy was used. An Arg/Arg genotype in patients on regularly scheduled β2 agonist therapy resulted in a gradual decline in morning peak expiratory flow (AM PEF) over the 16 weeks of evaluation, while no change in this parameter was observed in patients with a Gly/Gly genotype.9 In addition, AM PEF deteriorated substantially after cessation of treatment in the Arg/Arg patients receiving regularly scheduled inhaled β2 agonist therapy, but not in patients with a Gly/Gly genotype.9 There was no evidence that the codon 27 polymorphism influenced AM PEF in these patients. These data suggest that patients with a B2AR Arg/Arg16 genotype may be at risk for

In a recent study, the ABCB1 3435C>T polymorphism was found to be associated with significant differences in nelfinavir and efavirenz pharmacokinetics in HIV infected patients, and recovery of CD4 count was significantly greater and more rapid in patients with the TT genotype than patients with either CT or CC genotypes. Of all variables evaluated, only ABCB1 genotype and baseline HIV RNA copy number were significant predictors of CD4 recovery.10,11 Unfortunately, these investigators did not genotype for the ABCB1 1236C>T SNP so it remains unclear whether the 3435C>T is causative or in linkage with the causative SNP. This is the first evidence that a host genetic marker can predict immune recovery after ini-

Figure 3 The cytochromes P450 CYP3A4 and CYP3A5 genetic polymorphism. The top panel depicts the distribution of CYP3A4 activity in the white population, assuming that 10% of individuals express CYP3A4, with a 10-fold range of activity in the population. The middle panel depicts CYP3A5 expression, assuming that 25% of the white population express 3A5, with a 10-fold range of activity. The bottom panel depicts the CYP3A4 and CYP3A5 distributions (dashed lines) and the composite distribution for drugs metabolised equally well by both enzymes.
deleterious or non-beneficial effects of regularly scheduled inhaled β agonist therapy and may be candidates for alternative treatment or dosing schedules and/or earlier initiation of anti-inflammatory drugs. These results are consistent with the data described above for desensitisation of the β2 adrenoceptor in patients with a codon 16 Arg/Arg genotype. Although the codon 27 polymorphism does not seem to have a significant effect on inhaled β agonist therapy, an association between the codon 16 Gln/Gln genotype and an increased incidence of obesity has been observed. This relation seemed to be more prominent in men and could be overcome with exercise.

These B2AR SNPs are not the only SNPs found in the β adrenoceptor, with at least 13 distinct SNPs identified to date, leading to evaluation of B2AR haplotype structure compared with individual SNPs in determining receptor function and pharmacological response. While over 8000 B2AR haplotypes are theoretically possible, only 12 distinct haplotypes were observed among 77 subjects of various ethnic origin. Importantly, clinical evaluation of β agonist therapy in asthma patients revealed a better association of B2AR haplotype and bronchodilator response, than observed with any B2AR SNP alone. This is not surprising, as haplotype structure is often a better predictor of phenotypic consequences, which has led to the development of various methods to determine haplotype structure, some of which are comparatively simple to perform. It is likely that as more pharmacogenomic studies are conducted, haplotype structure will commonly emerge as the most informative genetic determinant of drug response.

**MOLECULAR DIAGNOSTICS FOR OPTIMISING DRUG THERAPY**

There is clearly great potential for pharmacogenomics to yield important new molecular diagnostics that will become routine clinical laboratory tests, by which physicians and pharmacists select drugs and doses for individual patients. Instead of using empirical treatment algorithms, pharmacogenomics can provide patient specific diagnostics to optimise drug treatment. Using the amount of DNA that can be isolated from a few millilitres of blood, it is possible to determine thousands of genotypes, and methodology is improving so rapidly that it will soon be straightforward to perform these tests in high throughput, automated systems, screening for thousands of SNPs in one test. This will be necessary, because most drug effects are polygenic in nature so treatment decisions will be based on a panel of SNPs. These genotyping results will not be reported as a list of SNPs, rather they will be interpreted for the clinician according to the patient’s diagnosis and treatment options. These new tests will not replace the more conventional biochemical tests that are currently used to assess organ function and disease status, rather they will provide additional tools for individualising and optimising drug therapy. Obviously, genotyping will not eliminate the need for follow up assessment of response, compliance with treatment, and other variables that influence treatment outcome. However, pharmacogenomics will make it increasingly possible to select the medications and doses that are optimal for each person, thereby improving efficacy and reducing toxicity. In this regard, it has been recently reported that among 27 drugs for which adverse events are frequently reported, a significantly higher percentage are metabolised by a polymorphic enzyme (59%) compared with randomly selected drugs (7%–22%). A substantial amount of work remains to be done, before the full clinical utility of pharmacogenomics can be fully appreciated and realised. While there are currently numerous examples that illustrate the potential, we are in the early days of deciphering the importance of genetic polymorphisms in determining drug response. Critical issues going forward include the fact that most drug effects are polygenic in nature, that haplotype structure is often more
informative than individual SNPs, and that functionally important polymorphisms can reside outside the coding or regulatory regions of genes. It is also important to recognise that clearly defined and objectively measured end points (that is, phenotypes) are essential to elucidate genotype-phenotype relations. In this regard, prospective clinical trials represent the ideal context within which pharmacogenomics of drug response are most likely to be elucidated. If done properly, ongoing research will change the practice of medicine and pharmacy, such that using genotype to individualise drug therapy will become the norm.

ACKNOWLEDGEMENT

Supported in part by the following NIH grants: R37 CA36401, R01 CA78224, U01 GM61393, U01 GM61394, Cancer Center support grant CA21765 and CA091842, by a Center of Excellence grant from the State of Tennessee, and by American Lebanese Syrian Associated Charities.

The author thanks Drs Howard McLeod, Julie Johnson, Eugene Krynetski, and Mary Relling for their many contributions and helpful suggestions during the preparation of this review.

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Gut 2003 52: ii10-ii18
doi: 10.1136/gut.52.suppl_2.ii10

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