PHARMACOGENOMICS: The Inherited Basis for Interindividual Differences in Drug Response

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Abstract It is well recognized that most medications exhibit wide interpatient variability in their efficacy and toxicity. For many medications, these interindividual differences are due in part to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and/or drug targets (e.g., receptors, enzymes). Pharmacogenomics is a burgeoning field aimed at elucidating the genetic basis for differences in drug efficacy and toxicity, and it uses genome-wide approaches to identify the network of genes that govern an individual's response to drug therapy. For some genetic polymorphisms (e.g., thiopurine S-methyltransferase), monogenic traits have a marked effect on pharmacokinetics (e.g., drug metabolism), such that individuals who inherit an enzyme deficiency must be treated with markedly different doses of the affected medications (e.g., 5%-10% of the standard thiopurine dose). Likewise, polymorphisms in drug targets (e.g., beta adrenergic receptor) can alter the sensitivity of patients to treatment (e.g., beta-agonists), changing the pharmacodynamics of drug response. Recognizing that most drug effects are determined by the interplay of several gene products that govern the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics research aims to elucidate these polygenic determinants of drug effects. The ultimate goal is to provide new strategies for optimizing drug therapy based on each patient's genetic determinants of drug efficacy and toxicity. This chapter provides an overview of the current pharmacogenomics literature and offers insights for the potential impact of this field on the safe and effective use of medications.

INTRODUCTION

There are often large differences among individuals in the way they respond to medications, whether the endpoint is host toxicity, treatment efficacy, or both. Potential causes for variability in drug effects include the nature and severity of the disease being treated, the individual's age and race, organ function, concomitant therapy, drug interactions, and concomitant illnesses. Although these factors are often important, inherited differences in the metabolism and disposition of drugs,
and genetic polymorphisms in the targets of drug therapy (e.g., receptors), can have an even greater influence on the efficacy and toxicity of medications. Clinical observations of inherited differences in drug effects were first documented in the 1950s (19, 60, 69), giving rise to the field of pharmacogenetics, which has now been rediscovered by the pharmaceutical industry and a broader spectrum of academia, giving birth to pharmacogenomics. Although the two terms are often used interchangeably, pharmacogenomics is used herein to describe a genome-wide approach to identifying the network of genes that govern an individual’s response to drug therapy. The ultimate goal of pharmacogenomics is to define the contributions of genetic differences in drug disposition or drug targets to drug response, thereby to improve the safety and efficacy of drug therapy through use of genetically guided, individualized treatment. With more sophisticated molecular tools available for detection of gene polymorphisms, advances in bioinformatics and functional genomics, and the wealth of new data emerging from the human genome projects, the genetic determinants of drug disposition and effects are being rapidly elucidated, and these data are already being translated into more rational drug therapy (40, 102, 104).

The elucidation of the molecular genetic basis for inherited differences in drug metabolism began in the late 1980s, with the initial cloning of a polymorphic human gene encoding the drug metabolizing enzyme debrisoquin hydroxylase (CYP2D6) (52). The human genes involved in many such pharmacogenetic traits have now been isolated, their molecular mechanisms elucidated, and their clinical importance more clearly defined, as highlighted herein. Inherited differences in individual drug metabolizing enzymes are typically monogenic traits, and their influence on the pharmacokinetics and pharmacologic effects of medications is determined by the importance of these polymorphic enzymes for the activation or inactivation of drug substrates. The effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (e.g., mercaptopurine, azathioprine, fluorouracil) (78) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (e.g., codeine) (30). Conversely, for drugs that have a very wide therapeutic index (e.g., metoprolol), the altered pharmacokinetics in CYP2D6-deficient individuals translates into clinically unimportant changes in drug effects.

However, the overall pharmacologic effects of medications are more often polygenic traits, determined by numerous genes encoding proteins involved in multiple pathways of drug metabolism, disposition, and effects (see Figure 1). Such polygenic traits are more difficult to elucidate in clinical studies, especially when a medication’s metabolic fate and mechanism(s) of action are poorly defined. However, as the molecular mechanisms of pharmacologic effects, genetic determinants of disease pathogenesis, and polymorphisms in genes that govern drug metabolism and disposition are clarified, these genetic determinants become more tractable. Furthermore, the human genome project, coupled with functional genomics, bioinformatics, and high-throughput screening methods, is providing powerful tools for elucidating polygenic determinants of disease pathogenesis and drug response.
Figure 1  The potential polygenic nature of drug response is illustrated, depicting the hypothetical effects of two polymorphic genes, one determining the extent of drug inactivation and the other, drug receptor sensitivity. The polymorphic drug metabolizing enzyme, which exhibits codominant inheritance in this example, determines drug concentrations in individual patients, whereas the polymorphic receptor determines drug response at any given drug concentration. Thus, in this example, an individual with homozygous wild-type drug metabolism and drug receptors would have a high probability of therapeutic efficacy and a low probability of toxicity (therapeutic ratio = 75), in contrast to an individual with homozygous mutant genotypes for the drug metabolizing enzyme and the drug receptor, in whom the likelihood of efficacy is low and toxicity high (therapeutic ratio = <0.13). [Modified from (40)]

Pharmacogenomics aims to elucidate the network of genes that determine the efficacy and toxicity of specific medications and to capitalize on these insights to discover new therapeutic targets and optimize drug therapy. Such knowledge should make it possible to select drug therapy based on each patient’s inherited ability to metabolize, eliminate, and respond to specific medications.

GENETIC POLYMORPHISMS IN DRUG METABOLISM AND DISPOSITION

Initially, inherited differences in drug metabolism were discovered following clinical observations of marked interindividual differences in drug response (e.g., pronounced hypotension following debrisoquin) (94). These observations were
then followed by population studies of drug disposition phenotype, then biochemical, and eventually molecular elucidation of the genetic defect responsible for the phenotypic outliers. This clinically based approach made it likely that such genetic polymorphisms would have clinical consequences for drug effect because their discovery was based on a clinical phenotype. However, the framework for discovery of genetic polymorphisms of drug disposition or response is evolving. With recent advances in molecular sequencing technology, gene (DNA) polymorphisms may be the initiating discoveries, with subsequent biochemical and finally clinical studies to assess whether the genomic polymorphisms have phenotypic consequence in patients (Figure 2). This latter framework may allow for the clarification of polymorphisms in drug metabolizing enzymes that have more subtle, yet important, consequences for interindividual variability in human drug response (Figure 3). Such polymorphisms may or may not have clear clinical

**Figure 2** Two strategies for the discovery of pharmacogenetic traits: The “pre-genomics” strategy (before 2000) was first to discover an unusual drug response or drug metabolism phenotype, and then to conduct family studies to elucidate inheritance patterns. These steps were followed by cloning of the involved gene and sequencing to identify genotypes that conferred the inherited phenotype. The “post-genomics” strategy (beginning in ~2000) capitalizes on high-throughput sequencing methods and databases generated from the human genome project, to first identify mutations [e.g., single nucleotide polymorphisms (SNPs)], and then search for associations with drug response phenotypes, without necessarily knowing a priori the mechanisms involved in potential genotype-phenotype associations (from 102).
Character of Population Phenotype Distributions Differs Based on Mutation Type

Figure 3  The left panel depicts the population distribution of drug metabolism phenotypes for most of the common genetic polymorphisms identified to date, which largely involve mutations that confer complete or near-complete loss of enzyme activity. The right panel depicts the population distribution of drug metabolism phenotypes for mutations associated with altered enzyme activity but not compete loss of function, reflecting the normal distribution of activity that typifies the metabolism and clearance of most medications. It is anticipated that at least some of the variability associated with the range of activity within a normal distribution will be inherited and due to mutations in the promoter regions of involved genes or amino acid changes that decrease or increase activity, but that do not eliminate activity (Adapted from M. Relling, personal communication).

significance for affected medications, depending on the importance of the enzyme for the overall metabolism of a medication, the expression of other drug metabolizing enzymes in the patient, the therapeutic index of the drug, the presence of concurrent medications or illnesses, and other polygenic factors that impact drug response. It is likely that almost every gene involved in drug metabolism is subject to genetic polymorphisms, although the phenotypic consequences may be subtle, such as placing individuals on one end or the other of a normal distribution of drug metabolism phenotypes, instead of conferring a complete deficiency of the encoded enzyme (Figure 3). Thus, inactivating polymorphisms can be broadly categorized into two groups, those that confer complete or near-complete loss of activity of encoded proteins and those that confer more subtle changes in function via more modest changes in expression, regulation, stability, or catalytic activity, but without complete loss of function.

For drug metabolizing enzymes, the molecular mechanisms of inactivation include splice site mutations resulting in exon skipping (e.g., DPD, CYP2C19),
microsatellite nucleotide repeats (e.g., CYP2D6), gene duplication (e.g., CYP2D6), point mutations resulting in early stop codons (e.g., CYP2D6), enhanced proteolysis (e.g., TPMT), altered promoter functions (e.g., CYP2A5, UGT1A1), critical amino acid substitutions (e.g., NAT2, CYP2D6, CYP2C19, CYP2C9), or large gene deletions (e.g., GSTM1, CYP2D6). Conversely, gene duplication can be associated with enhanced activity for some drug metabolizing enzymes (e.g., CYP2D6). For many genes encoding drug metabolizing enzymes, the frequency of single nucleotide polymorphisms (SNPs) and other genetic defects appears to be more common than the "1 per 1000 nucleotide" frequency that is frequently cited for the human genome [recently revised to $\sim 1$ SNP per 1900 bases in the human genome, with 1 SNP per $\sim 10^{8}$ bases in exons (61a)]. It may be that genetic polymorphisms of drug metabolizing enzymes are quite common because these enzymes are not essential from an evolutionary perspective. However, some essential receptors have more mutations than would be predicted from the 1 in 1000 rate (e.g., B1AR, B2AR), although these mutations do not confer complete loss of receptor function. Nonetheless, these common polymorphisms in drug receptors and drug metabolizing enzymes are often major determinants of interindividual differences in drug response.

No completely inactivating mutations have been reported for the gene encoding CYP3A4, which may be because CYP3A4 is required for the metabolism of critical endogenous glucocorticoid and sex hormones and thus its complete inactivation may be incompatible with life. However, a common polymorphism in the promoter for CYP3A4 (CYP3A4*1B) has been described (122) that may affect the extent to which CYP3A4 is inducible, rather than affecting constitutive levels of the enzyme, or its importance may be that it is in linkage disequilibrium with other functional polymorphisms at the CYP3A locus (80). Allelic variants have also been identified (CYP3A4*2, CYP3A4*3), one of which (CYP3A4*2) has altered catalytic activity for nifedipine but not testosterone (131). Furthermore, a polymorphism recently discovered in intron 3 of the human CYP3A5 gene creates an ectopic splice site, leading to a premature codon in the encoded mRNA. This common allelic variant (CYP3A5*3) is the principal genetic basis for polymorphic CYP3A5 expression in humans (80). Because most CYP3A4 substrates are also substrates for CYP3A5, this CYP3A5 polymorphism influences overall CYP3A activity in humans, which would be expected to shift subjects to the higher end of the population distribution for CYP3A activity (Figure 3, right panel).

Table 1 provides a list of human drug metabolizing enzymes that exhibit functional genetic polymorphisms, their substrates, and clinical consequences of polymorphisms in their genes, when applicable. Essentially all polymorphisms studied to date differ in frequency among ethnic and racial groups. Marked racial diversity in the frequency or type of functional defects in drug metabolizing enzymes means that the optional dose of medications may differ among world populations, an important consideration with the globalization of drug development.

Several adverse drug reactions have been linked to specific drug metabolizer phenotypes. Among the earliest examples are the associations of the slow
acetylator phenotype with isoniazid-induced neuropathies, hydralazine or procainamide-induced lupus, dye-associated bladder cancer, and sulfonamide-induced hypersensitivity reactions (53, 142). In each of these cases, acetylation of parent drug or an active metabolite was an inactivating pathway. N-acetyltransferase is a phase II enzyme that conjugates substrates with a more water-soluble small molecular moiety. Such conjugation reactions are frequently, but not always, detoxifying by “masking” a reactive functional group and typically enhancing urinary or biliary excretion of substrates.

Thiopurine S-methyltransferase (TPMT) is a polymorphic phase II enzyme that catalyzes the S-methyltransferase of thiopurine medications (mercaptopurine, thioguanine, and azathioprine), which is the inactivation pathway in hematopoietic tissues (78). For the TPMT polymorphism, all patients who inherit two non-functional TPMT alleles will develop dose-limiting hematopoietic toxicity that can be fatal if these patients are treated with full doses of thiopurine medications (39, 84, 103, 137). However, TPMT-deficient patients can tolerate thiopurine therapy, without acute toxicity, if they are treated with 5%--10% of the conventional dose of these medications. Ten percent of patients who are heterozygous at the TPMT locus (with one wild-type allele) are also at greater risk of thiopurine toxicity, but these patients can usually be safely treated with only modest dose reduction (11, 38b, 125). More recently, an adverse interaction was observed among the TPMT polymorphism, thiopurine therapy, and cranial irradiation (126). Among patients cured of acute lymphoblastic leukemia (ALL) with therapy that included concurrent thiopurine chemotherapy and cranial irradiation, those with TPMT-deficiency (heterozygous or homozygous deficient) had a significantly higher frequency of developing a malignant brain tumor as a consequence of ALL treatment (see Figure 4). In the absence of cranial irradiation, the incidence of brain tumors was essentially zero in patients treated with thiopurines, but in those who received cranial irradiation, the cumulative incidence of brain tumors was 40% in patients who were TPMT-deficient versus 8.3% in those with wild-type TPMT activity. Subsequent studies have begun to elucidate potential mechanisms by which high thioguanine levels perturb DNA repair mechanisms (77). These data illustrate the potential nature of interactions among genetic polymorphisms in drug metabolism, their drug substrates, and other components of treatment or the environment. The molecular genetic basis of the TPMT polymorphism has been clarified (79, 149, 150), and molecular diagnostics are now available to prospectively identify TPMT-deficient and heterozygotes patients (161).

Several phase I enzymes exhibit functional genetic polymorphism (Table 1), such that a subset of the population inherits a deficiency of the enzyme activity. These inherited deficiencies can be associated with increased pharmacologic effects for medications that are primarily inactivated by these enzymes, such as several tricyclic antidepressants and CYP2D6 (27), antipsychotics and CYP2D6 (27), fluoxetine and CYP2D6 (129), warfarin and CYP2C9 (3, 47, 146, 153), and 5-fluorouracil and dihydropyrimidine dehydrogenase (31, 51).
## Table 1 Genetic polymorphisms of human drug metabolizing enzymes and transporters

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrates</th>
<th>Consequences of polymorphism for drug effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I enzymes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td>Benzo(a)pyrene, phenacetin</td>
<td>Not yet elucidated</td>
<td>(20, 48, 71, 93)</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Acetaminophen, amonafide, caffeine, paraxanthine, ethoxyresorufin, propranolol, fluvoxamine</td>
<td>Not yet elucidated</td>
<td>(87)</td>
</tr>
<tr>
<td>CYP1B1</td>
<td>Estrogen metabolites</td>
<td>Not yet elucidated</td>
<td>(8)</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin, nicotine, halothane</td>
<td>Cigarette addiction</td>
<td>(90, 117)</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Cyclophosphamide, aflatoxin, mephenytoin</td>
<td>Not yet elucidated</td>
<td>(24)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Tolbutamide, warfarin, phenytoin, non-steroidal anti-inflammatory</td>
<td>Anticoagulant effect of warfarin</td>
<td>(3, 47, 146, 153)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Mephenytoin, omeprazole, hexobarbital, mepobarbital, propranolol, proguanil, phenytoin</td>
<td>Peptic ulcer response to omeprazole</td>
<td>(46, 50)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Beta blockers, antidepressants, antipsychotics, codeine, debrisoquin, dextromethorphan, encaainide, flecanide, fluoxetine, guanoxan, methoxy-amphetamine, N-propylajmaline, perhexiline, phenacetin, phenformin, propafenone, sparteine</td>
<td>Tardive dyskinesia from antipsychotics, narcotic side effects, efficacy, and dependence, imipramine dose requirement, beta blocker effect</td>
<td>(15, 17, 27, 30, 66, 70, 82, 86, 94, 118, 129, 140, 154, 163)</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>N-nitrosodimethylamine, acetaminophen, ethanol</td>
<td>Possible effect on alcohol consumption</td>
<td>(18, 41, 55, 88, 152)</td>
</tr>
<tr>
<td>CYP3A4/3A5/3A7</td>
<td>Macrolides, cyclosporin, tacrolimus, calcium channel blockers, midazolam, terfenadine, lidocaine, dapsone, quinidine, triazolam, etoposide, teniposide, lovastatin, alfentanil, tamoxifen, steroids, benzo(a)pyrene</td>
<td>Not yet elucidated, polymorphic 3A5 expression linked to 3A5 polymorphism</td>
<td>(43, 80, 122, 131)</td>
</tr>
<tr>
<td><strong>Aldehyde dehydrogenase (ALDH2)</strong></td>
<td>Cyclophosphamide, vinyl chloride</td>
<td>SCE frequency in lymphocytes</td>
<td>(159)</td>
</tr>
<tr>
<td><strong>Alcohol dehydrogenase (ADH3)</strong></td>
<td>Ethanol</td>
<td>Increased alcohol consumption and dependence</td>
<td>(55, 152, 158)</td>
</tr>
<tr>
<td><strong>Dihydropyrimidine dehydrogenase</strong></td>
<td>Phlorouracil</td>
<td>5-fluourouracil neurotoxicity</td>
<td>(31, 51)</td>
</tr>
<tr>
<td>NQO1 (DT-diaphorase)</td>
<td>Ubiquinones, menadione, mitomycin C</td>
<td>Menadione-associated urolithiasis</td>
<td>(127, 128, 136, 139)</td>
</tr>
</tbody>
</table>
### Phase II Enzymes

<table>
<thead>
<tr>
<th>Enzyme Type</th>
<th>Substrates/Reactions</th>
<th>Metabolism/Medication Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N-acetyltransferase (NAT1)</strong></td>
<td>P-aminosalicylic acid, p-aminobenzoic acid, sulfamethoxazole</td>
<td>Not yet elucidated (53, 142)</td>
</tr>
<tr>
<td><strong>N-acetyltransferase (NAT2)</strong></td>
<td>Isoniazid, hydralazine, sulfonamides, amonafide, procainamide, dapsone, caffeine</td>
<td>Hypersensitivity to sulfonamides, amonafide toxicity, hydralazine-induced lupus, isoniazid neurotoxicity (12, 38, 53, 60, 108, 142)</td>
</tr>
<tr>
<td><strong>Glutathione transferase GSTM1, M3, T1</strong></td>
<td>Aminochrome, dopachrome, adrenochrome and noradrenochrome</td>
<td>Not yet elucidated (7, 138, 160)</td>
</tr>
<tr>
<td><strong>Glutathione transferase GSTP1</strong></td>
<td>13-cis retinoic acid, ethacrylic acid, acrolein, epirubicin</td>
<td>Not yet elucidated (7, 21, 74, 132, 138, 160)</td>
</tr>
<tr>
<td><strong>Sulfotransferases</strong></td>
<td>Steroids, acetaminophen, estrogens, dopamine, epinephrine, naringenin</td>
<td>Not yet elucidated (121, 156)</td>
</tr>
<tr>
<td><strong>Catechol-O-methyltransferase</strong></td>
<td>Estrogens, levodopa, ascorbic acid</td>
<td>Substance abuse, levodopa response (123, 155)</td>
</tr>
<tr>
<td><strong>Histamine methyltransferase</strong></td>
<td>Histamine</td>
<td>Not yet elucidated (4, 58, 120)</td>
</tr>
<tr>
<td><strong>Thiopurine methyltransferase</strong></td>
<td>Mercaptopurine, thioguanine, azathioprine</td>
<td>Thiopurine toxicity and efficacy, risk of second cancers (1, 11, 39, 79, 83, 85, 124–126, 137, 161)</td>
</tr>
<tr>
<td><strong>UDP-glucuronosyl-transferase UGT1A1</strong></td>
<td>Irinotecan, bilirubin</td>
<td>Irinotecan glucuronidation (5, 10, 63)</td>
</tr>
<tr>
<td><strong>UDP-glucuronosyl-transferase UGT2Bs</strong></td>
<td>Opioids, androgens, morphine, naproxen, ibuprofen</td>
<td>Not yet elucidated (92)</td>
</tr>
</tbody>
</table>

### Transporters

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Substrates</th>
<th>Metabolism/Medication Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSEP</strong></td>
<td>Conjugates</td>
<td>Not yet elucidated (147)</td>
</tr>
<tr>
<td><strong>MDR-1</strong></td>
<td>Natural product anticancer drugs, CYP3A4 substrates, digoxin</td>
<td>Not yet elucidated (22, 75, 106, 134)</td>
</tr>
<tr>
<td><strong>MRPs</strong></td>
<td>Glutathione, glucuronide, and sulfate conjugates, nucleoside antivirals</td>
<td>Not yet elucidated (13, 26, 72, 135)</td>
</tr>
</tbody>
</table>
Interactions of Genetic Polymorphisms and Treatment May Result in Adverse Effects

A.

B.

several clinical studies have shown that the genetic polymorphism of \textit{CYP2C9} is a significant determinant of the dose of warfarin required for chronic anticoagulant therapy \cite{3, 47, 146, 153}. Patients who have inherited one or more variant \textit{CYP2C9} alleles (\textit{CYP2C9}*2 or \textit{CYP2C9}*3) require a significantly lower warfarin dose to maintain the target level of anticoagulation, and in some settings these variant alleles have been associated with a greater likelihood of bleeding complications \cite{3}. The potential seriousness of these polymorphisms is further exemplified by the fatal toxicity that occurred in a CYP2D6-deficient patient who received full doses of fluoxetine despite an inherited deficiency of CYP2D6, the primary inactivation pathway \cite{126}, and fatal hematopoietic toxicity in a TPMT-deficient heart transplant recipient treated with conventional dosages of azathioprine \cite{137}.

In addition to detoxifying and eliminating drugs and metabolites, drug-metabolizing enzymes may be required for activation of pro-drugs. For example, many opioid analgesics must be activated by CYP2D6 \cite{118}, rendering the 2\% to 10\% of the population who are homozygous for nonfunctional CYP2D6 alleles resistant to the analgesic effects of these medications. It is thus not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are prescribed across the population. There are also examples of variant alleles that confer increased enzyme activity, not enzyme deficiency. One such example is the \textit{CYP2D6}*2xN allele, which contains one to 13 duplications of a functional CYP2D6 gene, leading to significantly greater CYP2D6 activity and markedly higher dosage requirement for some medications that are metabolized by this enzyme (e.g., tricyclic antidepressants) \cite{27, 66}. Thus, genetic polymorphisms in drug metabolizing enzymes should be considered as a mechanism for either nonresponders or toxic responders in clinical trials.

In addition to optimizing the use of currently prescribed medications, pharmacogenomics may also offer new strategies and efficiencies in the drug development process. If nonresponders or toxic responders can be prospectively identified by genotyping, it may be possible to reduce the number of subjects needed in phase II–III clinical trials, by eliminating those who will not (cannot) respond due to inherited differences in drug metabolizing enzymes or drug targets \cite{44}.

\textbf{Figure 4} Inherited difference in drug metabolizing enzymes (DME) can alter the systemic exposure to affected substrates and thereby predispose to adverse interactions with other components of therapy. The top panel depicts such an interaction among the genetic polymorphism of TPMT, the affected thiopurine substrate (mercaptopurine), and concomitant treatment with cranial irradiation. Only those patients with ALL who were treated with cranial irradiation for CNS leukemia developed a subsequent malignant brain tumor 4–8 years after being cured of their ALL. However, as depicted in the bottom panel, the cumulative incidence of a brain tumor was significantly higher among patients who inherited a deficiency of TPMT (homozygous wildtype or heterozygous) and were treated with mercaptopurine concomitantly with their radiation therapy \cite{126}.
Figure 5  The potential of pharmacogenomics is to identify patients within a population with the same diagnosis (e.g., hypertension, leukemia, asthma, etc.), who are genetically predisposed either not to respond to therapy or to develop unacceptable toxicity, and then to prospectively alter their therapy to avoid treatment that is not likely to be optimal. The remaining, now more homogeneous population, can then be treated with conventional therapy in which they are not genetically predisposed to fail.

downside of this paradigm of drug development is that pretreatment screening would be necessary once a new drug is approved, and this would likely be stipulated as a requirement in the product labeling. The advantage, of course, would be that once marketed, such pretreatment testing would be able to target the new medication to those most likely to benefit (Figure 5).

GENETIC POLYMORPHISMS IN DRUG TRANSPORTERS

Although passive diffusion accounts for some drug and metabolite distribution, increased emphasis is being placed on the role of membrane transporters in absorption of oral medications across the gastrointestinal tract, excretion into the bile
and urine, distribution of drug into “therapeutic sanctuaries,” such as the brain and testes, and transport into sites of action, such as cardiovascular tissue, tumor cells, and infectious microorganisms. Many transporters include members of the adenosine triphosphate (ATP)-binding-cassette family, which share many physicochemical characteristics. Transporters include the P-glycoprotein (MDR1), alpha-1-acid glycoprotein, MRP1-6 (multidrug resistance proteins), and SPGP (sister PGP). It has been proposed that p-glycoprotein may not be essential for viability, because knockout mice appear normal until challenged with xenobiotics (134), whereas other transporters play critical roles in transport of endogenous substances, such as bilirubin and glutathione conjugates, and some medications (13). Although some polymorphisms in p-glycoprotein have been reported (106), and such variation may have functional significance for drug absorption and elimination, the clinical relevance of polymorphisms in drug transporters has yet to be fully elucidated.

Transporters for neurotransmitters (e.g., serotonin and dopamine, see Table 1) exhibit genetic polymorphism (35, 45), and some of these have been linked to drug response (e.g., clozapine response in schizophrenia has been linked to six genetic polymorphisms in four human genes, including the serotonin transporter) (6).

**DRUG TARGET PHARMACOGENETICS AND PHARMACOGENOMICS**

In recent years, there has been an increasing focus on genetic polymorphisms in drug targets, with an interest in defining their impact on drug efficacy and/or toxicity. For the purposes of this review, a drug target is defined as the direct protein target of a drug (e.g., a receptor or enzyme), proteins involved in the pharmacologic response (e.g., signal transduction proteins or downstream proteins), or proteins associated with disease risk or pathogenesis that is altered by the drug. The broad objective of drug target pharmacogenomics research is to identify the inherited basis for interindividual variability in drug response and toxicity, particularly when this variability is not explained by differences in drug concentration (pharmacokinetics).

Although studies of drug metabolism pharmacogenetics date back to the 1950s, the literature on drug target pharmacogenetics essentially began in the mid to late 1990s. Moreover, drug target pharmacogenomics is rapidly moving from a monogenic to a polygenic (genomic) focus, largely because most drug effects are polygenic in nature, and tools are now available for high throughput genotyping. Herein, we describe examples of drug target pharmacogenomics from each of the drug target categories defined above, and we discuss the rationale and benefits of moving from a single gene approach to a genomic strategy in order to provide more clinically useful information.

Most of the early drug target pharmacogenetic studies focused on a single polymorphism in a single gene, with the gene most often being the direct target of the drug (i.e., the receptor). Table 2 lists examples of genetic polymorphisms
<table>
<thead>
<tr>
<th>Gene/gene product</th>
<th>Medication</th>
<th>Drug effect associated with polymorphism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>ACE inhibitors (e.g., enalapril)</td>
<td>Renoprotective effects, BP reduction, left ventricular mass reduction, endothelial function improvement, ACE inhibitor induced cough</td>
<td>(64, 76, 111, 112, 115, 116, 119, 130, 143)</td>
</tr>
<tr>
<td>Bradykinin B2 receptor</td>
<td>ACE inhibitors</td>
<td>ACE inhibitor induced cough</td>
<td>(107)</td>
</tr>
<tr>
<td>$\beta_2$-adrenergic receptor</td>
<td>$\beta_2$-agonists (e.g., albuterol, terbutaline)</td>
<td>Bronchodilation, susceptibility to agonist-induced desensitization, cardiovascular effects (e.g., increased heart rate, cardiac index, peripheral vasodilation)</td>
<td>(23, 34, 54, 59, 62, 89, 99, 151)</td>
</tr>
<tr>
<td>$\alpha$-blockers (e.g., metoprolol)</td>
<td>$\beta$-blockers (e.g., metoprolol)</td>
<td>Antihypertensive effect</td>
<td>(65)</td>
</tr>
<tr>
<td>ACE</td>
<td>Fluvastatin</td>
<td>Lipid changes (e.g., reductions in total LDL-cholesterol and apolipoprotein B); progression/regression of atherosclerotic lesions</td>
<td>(96)</td>
</tr>
<tr>
<td>Platelet FC receptor (FCRII)</td>
<td>Heparin</td>
<td>Heparin-induced thrombocytopenia</td>
<td>(14)</td>
</tr>
<tr>
<td>Glycoprotein IIIa subunit of glycoprotein IIb/IIIa receptor</td>
<td>Aspirin/glycoprotein IIb/IIIa inhibitors (e.g., abciximab)</td>
<td>Antiplatelet effect</td>
<td>(105)</td>
</tr>
<tr>
<td>ALOX5</td>
<td>Leukotriene biosynthesis inhibitors (e.g., ABT-761-zileuton-derivative)</td>
<td>Improvement in FEV$_1$</td>
<td>(32)</td>
</tr>
<tr>
<td>Receptor/Receptor</td>
<td>Drug/Agent(s)</td>
<td>Effect/Condition</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Conjugated estrogens</td>
<td>Bone mineral density increases</td>
<td>(113)</td>
</tr>
<tr>
<td>Sulfonylurea receptor</td>
<td>Sulfonylureas (e.g., tolbutamide)</td>
<td>Sulfonylurea-induced insulin release</td>
<td>(56)</td>
</tr>
<tr>
<td>Inositol-p1p</td>
<td>Lithium</td>
<td>Response of manic depressive illness</td>
<td>(145)</td>
</tr>
<tr>
<td>Dopamine receptors (D2, D3, D4)</td>
<td>Antipsychotics (e.g., haloperidol, clozapine, thioridazine nemorapride)</td>
<td>Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3), hyperprolactinemia in females (D2)</td>
<td>(6, 9, 25, 36, 61, 68, 133, 148)</td>
</tr>
<tr>
<td>Dopamine receptor</td>
<td>Levodopa &amp; dopamine</td>
<td>Drug induced hallucinations</td>
<td>(95)</td>
</tr>
<tr>
<td>5HT2A, 5HT6</td>
<td>Antipsychotics (e.g., clozapine, typical antipsychotics)</td>
<td>Clozapine response (5HT2A, 5HT6), typical antipsychotic response and long term outcomes (5HT2A)</td>
<td>(67, 100, 162)</td>
</tr>
<tr>
<td>G protein β3</td>
<td>Antidepressants (various)</td>
<td>Response to antidepressant therapy</td>
<td>(164)</td>
</tr>
<tr>
<td>Serotonin transporter (5-HTT)</td>
<td>Antidepressants (e.g., clomipramine, fluoxetine, paroxetine, fluvoxamine)</td>
<td>5-HT neurotransmission, antidepressant response</td>
<td>(73, 141, 157)</td>
</tr>
<tr>
<td>Ryanodine receptor</td>
<td>Anesthetics (e.g., halothane)</td>
<td>Malignant hyperthermia</td>
<td>(101)</td>
</tr>
</tbody>
</table>
of drug targets that have been investigated for their contribution to drug response variability, and it summarizes the relevant drug (drug class) and the drug response or adverse effect associated with the polymorphism. Review of this body of literature reveals that although single gene/single polymorphism drug target studies have identified numerous associations between polymorphisms and the anticipated response, they have also been somewhat disappointing in terms of the consistency with which these associations have been documented. For example, the insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene is probably one of the most extensively studied of the drug target polymorphisms. The DD genotype has been consistently associated with increased ACE activity and ACE I/D genotypes have been associated with various clinical effects of ACE inhibitors, including renoprotective effects, blood pressure reduction, left ventricular hypertrophy reduction, and improvements in endothelial function. However, these studies are not concordant, in that some show no association between response and ACE I/D genotype (16), some show the II genotype is associated with greater drug response (64, 76, 111, 112, 115), whereas others show the DD genotype is associated with the best response (57, 116, 119, 130, 143).

The β2-adrenergic receptor polymorphisms and their influence on β2-agonist-mediated effects have also been the focus of numerous investigations. Studies of the bronchodilator effects of β2-agonists have been equivocal, with some showing the β2-agonist-mediated bronchodilator effects are dependent on a certain genotype or allele, whereas others have reported that the opposite genotype/allele is a predictor of response (34, 62, 89, 99, 151). Studies of the cardiovascular effects of β2-agonists are also conflicting (23, 54, 59). Like many genes, the β2-adrenergic receptor gene has multiple polymorphisms, some of which are in linkage disequilibrium. Recent studies suggest that analysis of haplotype, rather than analysis of individual polymorphisms, may markedly enhance the ability to detect important associations between gene polymorphisms and drug response (34).

Numerous studies have also focused on polymorphisms in various genes that are direct targets of psychiatric medications, particularly polymorphisms in the dopamine receptor genes and the serotonin (5HT) receptor genes (6, 25, 36, 61, 67, 68, 73, 100, 133, 144, 148, 157, 162). Consistent with the ACE and β2-adrenergic receptor gene polymorphisms, the 5HT receptor genetic polymorphisms have been associated in some, but not all, studies with efficacy or toxicity. The serotonin transporter is the only example in Table 2 where multiple studies have consistently shown an association between response and genotype. Such apparent discordance among studies may reflect the endpoints utilized to measure drug effects, the time course over which effects were assessed, the nature of the study population, and other biological (e.g., genetic) or environmental differences among studies.

Although focusing on a polymorphism in a direct protein target of a drug may seem a logical approach, it is also easy to explain why such an approach may lead to equivocal results, and why a genomic approach may provide more reproducible results. Take the ACE inhibitors as an example. ACE is the direct protein target
of the ACE inhibitors. Inhibition of ACE decreases production of angiotensin II and decreases degradation of bradykinin and other vasodilator substances, each having their own signal transduction cascade. Angiotensin II, for example, binds to its G protein coupled receptor (AT), with the ensuing signal transduction cascade, ultimately involving 20 to 30 proteins to generate the eventual cellular effects. Given estimates that polymorphisms occur about every 1900 bp (61a), it would be anticipated that, on average, the genes for each of these 20–30 proteins could have one or two polymorphisms. Therefore, it is easy to appreciate why a single polymorphism in the ACE gene may not adequately predict the variability in patient response to ACE inhibitors. Given that most drugs act on enzymes or receptors that have similar or more complex signal transduction cascades, it seems apparent that genomic approaches will be needed to more adequately elucidate the genetic basis for drug response variability.

Table 3 summarizes single gene/single polymorphism pharmacogenetic studies focused on polymorphisms that are associated with altered disease risk. Unlike many of the single gene/direct target pharmacogenetic studies, the findings in this category have been more consistent across studies. The first examples in Table 3 highlight how a drug known to cause a certain adverse event, in combination with a genetic polymorphism associated with the same adverse event, can lead to a marked increase in the risk of drug toxicity. For example, oral contraceptive use in patients with Factor V or prothrombin mutations produces a markedly higher risk of a thrombotic event than either the mutation alone or oral contraceptive use alone (97, 98). Similarly, gene mutations in cardiac potassium and sodium channels that are associated with long QT syndrome are also associated with increased risk of drug-induced Torsade de Pointes (2, 33, 109). This may represent a useful paradigm for identifying patients at greatest risk of serious drug-induced adverse effects.

Methylation of cytosines within CpG-rich regions of human gene promoters is a well-established mechanism of transcriptional inactivation. It was recently shown that interindividual differences in methylation of the promoter region of O6-methylguanine-DNA methyltransferase (MGMT) are significantly related to the response of grade III–IV gliomas to carmustine therapy (37). Responses were documented in 12 of 19 patients with methylated MGMT promoters in their tumors, compared to responses in only 1 of 28 patients with unmethylated MGMT promoters (37). The putative mechanism is that those with methylated MGMT promoters had lower expression of MGMT, an enzyme that reverses the alkylation of DNA that is critical to the mechanism of carmustine’s anticancer effects. Future studies are needed to verify these initial findings, determine the precise mechanism(s) involved, and clarify the molecular basis for interindividual differences in MGMT promoter methylation.

The remaining examples in Table 3 highlight how disease-associated polymorphisms may also impact drug efficacy, even when the proteins of interest are not directly involved in the pharmacologic actions of the drug. The outcome literature with HMG CoA-reductase inhibitors (statins) are particularly interesting in this regard. Studies of the statins that were conducted in fairly large populations with
**TABLE 3** Disease pathogenesis polymorphisms associated with altered drug effect

<table>
<thead>
<tr>
<th>Gene/gene product</th>
<th>Disease or response association</th>
<th>Medication</th>
<th>Impact of polymorphism on drug effect/toxicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin and factor V</td>
<td>Deep vein thrombosis and cerebral vein thrombosis</td>
<td>Oral contraceptives</td>
<td>Increased deep vein and cerebral vein thrombosis risk with oral contraceptives</td>
<td>(97, 98)</td>
</tr>
<tr>
<td>HERG, KvLQT1, Mink, MiRP1</td>
<td>Congenital long QT syndrome</td>
<td>Various such as: erythromycin, terfenadine, cisapride, clarithromycin, antiarrhythmic drugs (e.g., quinidine)</td>
<td>Increased risk of drug-induced Torsade de Pointes</td>
<td>(2, 33, 109)</td>
</tr>
<tr>
<td>APOE</td>
<td>Atherosclerosis progression; ischemic cardiovascular events</td>
<td>Statins (e.g., simvastatin)</td>
<td>Enhanced survival prolongation with simvastatin</td>
<td>(29, 49, 110, 114)</td>
</tr>
<tr>
<td>APOE</td>
<td>Alzheimer's disease</td>
<td>Tacrine</td>
<td>Clinical improvement with tacrine</td>
<td>(42)</td>
</tr>
<tr>
<td>MGMT</td>
<td>Glioma</td>
<td>Carmustine</td>
<td>Response of glioma to carmustine</td>
<td>(37)</td>
</tr>
<tr>
<td>CETP</td>
<td>Atherosclerosis progression; HDL-cholesterol levels</td>
<td>Statins (e.g., pravastatin)</td>
<td>Slowing atherosclerosis progression by pravastatin</td>
<td>(81)</td>
</tr>
<tr>
<td>Stromelysin-1</td>
<td>Atherosclerosis progression</td>
<td>Statins (e.g., pravastatin)</td>
<td>Reduction in cardiovascular events by pravastatin (e.g., death, myocardial infarction, stroke, angina, etc.), reduction in repeat angioplasty</td>
<td>(28)</td>
</tr>
<tr>
<td>Parkin</td>
<td>Parkinson’s disease</td>
<td>Levodopa</td>
<td>Clinical improvement and L-dopa induced dyskinesias</td>
<td>(91)</td>
</tr>
</tbody>
</table>
specific clinical endpoints (beyond lipid changes) have focused on the polymorphic genes coding the following proteins: apolipoprotein E, cholesteryl ester transfer protein (CETP), stromelysin-1, and β-fibrinogen (28, 29, 49, 81, 110, 114). These studies and their results have been strikingly consistent. First, investigators studied a genetic polymorphism thought to be or documented as associated with an adverse clinical outcome (e.g., greater atherosclerosis progression, cardiovascular event, or death), but not directly associated with the drug’s pharmacologic effect. In all cases, the placebo arm of the study supported this genotype-clinical outcome association. The studies were also remarkably consistent in showing that those who carried the polymorphism associated with increased risk of adverse outcomes were the patients who derived the greatest benefit from statin therapy, whereas the lower risk group derived less or no benefit from the statin. These studies also consistently showed that lipid changes associated with statin therapy did not differ by genotype, suggesting that the clinical benefits are somewhat independent of lipid lowering and thus independent of the presumed direct pharmacological action of the drugs. Similar findings have been documented with apolipoprotein E polymorphisms and tacrine response in Alzheimer’s disease (42) as well as parkin polymorphisms and efficacy or adverse effects of levodopa therapy in Parkinson’s disease (91).

Polymorphisms in the genes of pathogenic agents (notably HIV and Helicobacter pylori, among others) are also important determinants of response to antinfec-tive agents. However, these pharmacogenetic examples are not discussed here, as the focus of this review is human and not pathogen polymorphisms.

In many ways, the single polymorphism/single gene studies described above provide a “proof of concept,” specifically that variability in drug response might be attributable to genetic variability. Although these studies have documented that some variability in drug response can be explained by genetic variability, they do not always provide a level of predictability that could be useful clinically. For example, the apolipoprotein E-tacrine response in Alzheimer’s is one of the most widely cited pharmacogenomic studies (42). Although the authors provide clear evidence of a difference in response to tacrine based on genotype, the predictive value is not adequate to withhold therapy based on genotype alone, especially in this setting where there are few alternative drug therapy choices. For example, 83% of patients lacking the APO ε4 allele had a positive response to tacrine, whereas only 41% of patients with an APO ε4 allele had a positive response. Thus, even with these clear response differences by genotype, it would not be appropriate to withhold therapy based on the presence of the APO ε4 allele because a substantial portion of patients with this allele do benefit from such therapy. In fact, the greatest improvement with tacrine in this study was observed in a patient carrying an APO ε4 allele. Moreover, the difference in response between genotypes for most of the other examples cited above are much less dramatic than the tacrine-APO ε4 example. Thus, to move drug target pharmacogenomics to the next level, where genetic information can be used to reliably predict drug response (or toxicity), with subsequent therapeutic decisions based on this information, more sophisticated genomic approaches will be necessary in most cases.
Although there are only a few examples of genomic approaches that relate drug target polymorphisms to response or toxicity, the available studies suggest that such approaches will provide more useful information than the single gene/single polymorphism approach. One approach is a “candidate gene” pharmacogenomic approach, where polymorphisms in multiple genes known or suspected to contribute to drug effects or disposition are studied for their association with response or toxicity.

For example, a recent study of clozapine response in schizophrenic patients used a multiple candidate gene approach to gain insight into the genetic contribution to response variability to clozapine (6). This study evaluated the relationship between clozapine response and 19 polymorphisms in 10 genes (including genes for \( \alpha \)-adrenergic receptors, dopamine receptors, serotonin receptors, histamine receptors, and the serotonin transporter). A combination of the six polymorphisms showing the strongest association with response provided a positive predictive value of 76%, a negative predictive value of 82%, with a sensitivity of 96% for identifying schizophrenic patients showing improvement with clozapine, and a specificity of 38% for identifying patients with minimal response to clozapine. Additional studies will be needed to validate this model in a larger patient population, to assess their ability to predict response to other antipsychotic agents (or even placebo), and to expand the repertoire of genes and polymorphisms investigated. Although the approaches described above can probably be improved upon, it provides insights into an approach that is likely to prove much more powerful in the quest to move pharmacogenomics into the clinical setting.

Another approach in pharmacogenomics is a genome scanning approach, which does not rely on knowledge of the drug’s pharmacologic actions, as does the candidate gene approach. Use of SNP maps to identify polymorphisms in genes involved in drug disposition or effects, or in linkage disequilibrium with these polymorphisms, and thereby associated with efficacy or toxicity, is a pharmacogenomics approach that many large pharmaceutical companies plan to employ in their drug development process. Actual implementation of such an approach may further advance our understanding of the genetic basis for variability in drug efficacy and toxicity, although the mechanism underlying such associations will require further study once the predictive SNPs have been identified. For this to be a cost-effective strategy, the cost of SNP detection will have to decrease markedly, or the number of SNPs tested will have to be constrained well below the estimated 1.42 million SNPs in each human genome (61a).

THE FUTURE

It is clear from the numerous examples reviewed here that genetic polymorphism can be an important determinant of drug disposition and response in humans. It is equally clear that we are at the early stages of defining these pharmacogenomic
Ultimately, a secured online database should be developed in which each individual’s informative genetic profile will be stored and available to authorized clinicians. With current technologies, these informative pharmacogenomic genotypes will likely be determined in panels that are potentially important for their current illness, but with advances in genotyping technologies, it should eventually be possible to perform genome-wide detection of hundreds of thousands of informative mutations and to deposit these data well prior to the need to make treatment decisions.

Figure 6  Ultimately, a secured online database should be developed in which each individual’s informative genetic profile will be stored and available to authorized clinicians. With current technologies, these informative pharmacogenomic genotypes will likely be determined in panels that are potentially important for their current illness, but with advances in genotyping technologies, it should eventually be possible to perform genome-wide detection of hundreds of thousands of informative mutations and to deposit these data well prior to the need to make treatment decisions.

determinants and that a broader genomics approach will be required to elucidate polygenic determinants for most medications. Once the network of genes that govern drug responses in humans is defined, it will then be possible to more accurately optimize drug therapy based on each patient’s ability to metabolize, transport, and respond to medications. The vision is that in the future, authorized clinicians will be able to access a secured database in which their patient’s genetic polymorphisms will have been deposited, as they are determined for specific classes of medications, based on their illnesses (Figure 6). Technology will ultimately make it possible to perform a focused genome-wide scan for polymorphisms that are associated with disease risk or drug response, such that these data will be determined a priori and thus will be available to clinicians for preventive health and prospective treatment decisions. The end result will be the optimal selection of medications and their dosages based on the individual patient and not treatment based on the average experience from the entire universe of patients with a similar diagnosis.
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