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PHARMACOGENOMICS AND INDIVIDUALIZED DRUG THERAPY

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■ **Abstract** Pharmacogenetics deals with inherited differences in the response to drugs. The best-recognized examples are genetic polymorphisms of drug-metabolizing enzymes, which affect about 30% of all drugs. Loss of function of thiopurine S-methyltransferase (TPMT) results in severe and life-threatening hematopoietic toxicity if patients receive standard doses of mercaptopurine and azathioprine. Gene duplication of cytochrome P4502D6 (CYP2D6), which metabolizes many antidepressants, has been identified as a mechanism of poor response in the treatment of depression. There is also a growing list of genetic polymorphisms in drug targets that have been shown to influence drug response. A major limitation that has heretofore moderated the use of pharmacogenetic testing in the clinical setting is the lack of prospective clinical trials demonstrating that such testing can improve the benefit/risk ratio of drug therapy.

INTRODUCTION

Most patient populations show large interindividual variability in drug response and toxicity. For all major classes of drugs (ACE inhibitors, β-adrenoreceptor antagonists, selective serotonin reuptake inhibitors, tricyclic antidepressants, statins, and β-agonists) given at standard doses, a substantial proportion of patients do not respond, respond only partially, or experience adverse drug reactions (ADRs). Drug concentrations in plasma can vary more than 600-fold between two individuals of the same weight on the same drug dosage. This variation can be of genetic, physiological, pathophysiological, or environmental origin, but a drug's absorption, distribution and metabolism, and interactions with its target can be determined by genetic differences. In general, genetic factors are estimated to account for 15%–30% of interindividual differences in drug metabolism and response, but for

certain drugs or classes of drugs, genetic factors are of utmost importance and can account for up to 95% of interindividual variability in drug disposition and effects (1–3).

The idea that drug response is determined by genetic factors that alter the pharmacokinetics and pharmacodynamics of medications evolved in the late 1950s, when an inherited deficiency of glucose-6-phosphate dehydrogenase was shown to cause the severe hemolysis observed in some patients exposed to the antimalarial primaquine (4). This discovery explained why hemolysis was observed mainly in African-Americans, in whom the deficiency is common, and rarely in Caucasians of Northern, Western, and Eastern European descent. In 1959, Vogel coined the term pharmacogenetics to describe inherited differences in drug responses (5). The term pharmacogenomics was introduced to reflect the recent transition from genetics to genomics and the use of genome-wide approaches to identify genes that contribute to a specific disease or drug response. A pharmacogenomics approach may allow a specific drug therapy to be targeted to genetically defined subsets of patients and may lead to a new disease and treatment classification at the molecular level. Moreover, identification of new disease genes may provide new drug targets. For the 30,000 known diseases, including 100 to 150 major common diseases, no drug treatment exists or improved drug treatment is needed (6).

Severe ADRs such as hepatotoxicity or drug-induced arrhythmias continue to be significant problems for many new drugs during the development and postmarketing phases. ADRs increase morbidity and mortality and are associated with considerable cost to the health care system. They may be responsible for $>100{,}000$ deaths yearly in the United States and account for $\sim$5% of all hospital admissions (7). Genetic factors play a role in the pathogenesis of predictable ADRs, and basing drug therapy on patients' individual genetic make-up may result not only in an improved response but also in a clinically important reduction in ADRs. For example, of 27 drugs frequently cited in ADR studies, 59% are metabolized by at least one enzyme with a variant allele associated with decreased drug metabolism (8). Conversely, only 7%–20% of randomly selected drugs are metabolized by enzymes known to exhibit functional genetic polymorphisms. Genetic variability in drug-metabolizing enzymes may therefore be an important contributor to the incidence of ADRs. Indeed, genetic susceptibility is implicated in various idiosyncratic ADRs, including hypersensitivity to abacavir (9), Stevens-Johnson syndrome induced by carbamazepine (10), and severe cutaneous ADRs caused by allopurinol (11).

With the complete sequence of the human genome available, individualized medicine may soon become reality. Genomic information may allow more accurate prediction of an individual's drug response and selection of the appropriate drug dosage to achieve the optimal therapeutic response, avoid therapeutic failure, and minimize side effects and toxicity. Such information is of utmost importance during drug development. About 4% of all new medications are withdrawn because of ADRs (12), and failure of a newly released drug is disastrous for a pharmaceutical

company, which may have spent more than a billion dollars to develop that single product.

Although many genes encoding proteins involved in the metabolism, transport, and mechanism of action of medications are known to exhibit polymorphism in humans, use of this knowledge in routine clinical practice is limited. Excepting a few examples of drug-metabolizing enzymes, the contribution of genetic polymorphisms to individual differences in drug effects and toxicity is not well understood. Moreover, most studies have focused on the effect of a single polymorphism on drug response. This approach neglects the fact that drug-response phenotype, like most disease phenotypes, is a complex polygenic trait also determined by nongenetic factors (3) (Figure 1). The extent to which genetic factors contribute to the drug-response/toxicity phenotype depends on the extent of the candidate gene's influence on drug disposition and effects. Misconceptions also exist about the information provided by a pharmacogenetic test. Even if a gene has a large effect on a drug's pharmacokinetics or pharmacodynamics, the presence of a single-nucleotide polymorphism (SNP) in that gene will not provide an unequivocal answer but, rather, will indicate the likelihood that an individual patient will show an altered drug response. The highest positive predictive value of a genetic test will be observed for genes with a major effect. Genetic polymorphisms that lead to a loss of function of drug-metabolizing enzymes will result in higher drug concentrations. If such concentrations are associated with a high probability of drug toxicity, a patient who has this genotype is highly likely to develop toxicity if given the same dose as patients who carry the wild-type allele of the gene. However, the negative predictive value (likelihood that a patient without the SNP will not have toxicity) will be poor if nongenetic factors leading to high drug concentrations are neglected (e.g., drug-drug interactions). If a patient who carries a wild-type allele is concomitantly treated with a drug that inhibits the enzyme, the patient will show a phenotype (high drug concentration) like that of patients with two nonfunctional alleles of the gene, a phenomenon called phenocopying. Neglecting the impact of nongenetic factors on a drug-response phenotype has led to claims that the presence of deficient alleles of thiopurine S-methyltransferase (TPMT) is a poor predictor of severe myelosuppression caused by the use of 6-mercaptopurine or azathioprine (13).

Clinical use of pharmacogenetic testing has been severely limited by a lack of prospective clinical trials. Such trials are required to establish that pharmacogenetic testing benefits the selection of the appropriate drug and dose for the individual patient, thereby improving therapeutic responses and/or reducing ADRs.

This review focuses on the potential therapeutic consequences of inherited differences in drug disposition and drug action and illustrates the potential of pharmacogenetics to improve the benefit/risk ratio of drugs. The best-studied examples of genetic polymorphisms that alter drug response are in genes that encode drug-metabolizing enzymes. Less extensively studied is the role of polymorphism of the genes encoding transporters, receptors, and signaling pathways, but there is growing evidence that these genes also alter drug response.

METABOLISM

Much phase I drug metabolism is performed by polymorphic enzymes, particularly various forms of cytochrome P450 (CYP) (14). This variability influences the bioavailability of many of the drugs in clinical use. The influence of genetic polymorphisms of drugs metabolized by CYP2C9, CYP2C19, and CYP2D6 indicates significant penetrance of these polymorphisms, affecting the metabolism of 20%–30% of clinically used drugs (15–17). Genetic polymorphism of several phase II enzymes, including some relevant to cancer chemotherapy, is also important. Below, we provide several clinically important examples of polymorphism in metabolizing enzymes.

CYP2C9 and Warfarin Treatment

Warfarin is widely used as an oral anticoagulant. Major side effects are bleeding complications, whose estimated average annual frequencies are 0.6% (fatal), 3.0% (major), and 9.6% (minor) (18). In a prospective study, the frequency of severe bleeding after starting warfarin therapy was 3.0% during the first month, 0.8% per month during the remainder of the first year, and 0.3% per month after the first year (19). However, some patients are very sensitive to anticoagulant effects, even at a very low dose of warfarin.

Because required dosages of warfarin vary markedly (up to tenfold) and anticoagulative responses to warfarin vary unpredictably among individuals, it has been suggested that patients who carry the *2 and *3 alleles of polymorphic *CYP2C9* are more susceptible to bleeding complications with warfarin treatment. Warfarin is a racemate, and its S-enantiomer is five times more potent than its R-enantiomer. The S-enantiomer is mostly metabolized by CYP2C9 to the inactive 7-hydroxywarfarin (20); any change in the activity of CYP2C9 is likely to have a significant influence on the anticoagulative response.

Several clinical studies have investigated the influence of CYP2C9 polymorphisms on warfarin sensitivity and/or risk of overanticoagulation after initiation of therapy or long-term treatment (e.g., 21–26). Despite different study designs, the data clearly indicate that patients carrying at least one variant *CYP2C9* allele require lower maintenance doses and have a significantly higher risk of bleeding. A landmark study (22) compared frequencies of *CYP2C9* polymorphisms in three groups on warfarin: an anticoagulation clinic-based group requiring low doses and two control groups receiving a wide range of dosages. The frequency of homozygotes CYP2C9*2/*2 and *3/*3 was 0.7% in the combined control groups but 5.6% (only *2/*2) in the low-dose group. Compared with controls, the odds ratio of heterozygosity for *2 or *3 was 2.68 (95% CI, 1.22–5.86) and the odds ratio of homozygosity for *2 or *3 was 7.8 (95% CI, 1.90–32.1). The rate of life-threatening bleeding in the low-dose group was 3.7 times that of controls (95% CI, 1.4–9.5). Genotyping for *CYP2C9* before giving warfarin therapy and adjustment of dose for patients with variant *CYP2C9* alleles could therefore reduce severe bleeding

complications. Additional variability in warfarin's anticoagulant effects may be explained by polymorphisms in genes that encode clotting factors and warfarin targets, including the recently reported influence of polymorphisms in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1). Indeed, VKORC1 haplotype explained ~25% of the variance in warfarin, compared to 6%–10% for CYP2C9 alone (15, 27–29).

CYP2C19 and Proton Pump Inhibitor Therapy

Proton pump inhibitors (PPIs) are the drugs of choice for the acute and long-term treatment of gastric acid–related disorders such as peptic ulcer and gastroesophageal reflux disease and, combined with two or three antibiotics, for the eradication of *Helicobacter pylori* (Hp). PPIs in clinical use are omeprazole, its S-enantiomer esomeprazole, lansoprazole, pantoprazole, and rabeprazole (30).

All PPIs dose-dependently inhibit gastric acid secretion and raise intragastric pH for 24–48 h. Intragastric pH should be maintained above 3.5 to heal peptic ulcer and above 4 to heal gastroesophageal reflux disease. The area under the plasma-concentration-versus-time curve (AUC) is closely related to the inhibition of gastric secretion. Above an AUC value of ~3 μmol h/l, almost 100% inhibition of acid secretion is achieved (31, 32). These findings suggest that therapeutic efficacy depends on drug dose and dosing interval, but all regimens for Hp eradication are based on the same dose of PPI for all patients, assuming that the rate of drug elimination (mainly by hepatic metabolism) is essentially the same among patients.

Pronounced differences in PPI pharmacokinetics result in up to a 12-fold difference among patients. Hepatic metabolism of PPIs is catalyzed by CYP2C19 and, to a smaller extent, CYP3A4. Genetic polymorphism of *CYP2C19* manifests in three distinct phenotypes: the poor metabolizer (PM), the heterozygous extensive metabolizer (hetEM), and the extensive metabolizer (EM). PMs carry two nonfunctional alleles, hetEMs have one nonfunctional and one wild-type allele, and EMs are homozygous for the wild-type allele. Thus far, eight loss-of-function *CYP2C19* alleles have been reported, and pronounced ethnic differences exist in the frequencies of the nonfunctional alleles. The frequency is low, ranging from 1.2% to 3.8%, in Caucasian Europeans, but as high as 23% in Oriental populations (33, 34). The same dose of a PPI produces 3–12 times greater drug exposure in PMs than in EMs. HetEMs have 2–4 times higher AUC values than do homozygous EMs. These genotype-based differences in AUC translate into differences in the extent and duration of inhibition of gastric acid secretion. After a single 20-mg dose of omeprazole, the intragastric pH (median over 24 h) was 4.5 for PMs, 3.3 for hetEMs and 2.1 for EMs. In view of the close relationship between drug concentration and inhibition of acid secretion, the outcome of giving all patients the same dose to eradicate Hp and heal ulcers is likely to be significantly influenced by *CYP2C19* genotype (35, 36).

This contention is supported by several clinical studies of Hp eradication in which the *CYP2C19* genotype was retrospectively analyzed. The cure rates of Hp

infection were significantly lower in EMs than in hetEMs and PMs (35–41). Most treatment failures were observed in EMs. In one study (41), clear genotype-related differences were observed in the PPI concentrations at the end of the dose interval (PM, 753 ng/ml; hetEM, 59; EM, 21). Multivariate analysis showed that CYP2C19 polymorphism was the most important factor, apart from antibiotic resistance, influencing successful eradication. The difference in absolute risk between patients with the wild-type and variant alleles was ~20%. This study showed similar lansoprazole concentrations in EM patients regardless of Hp-eradication success; other factors modifying treatment response were bacterial strain, resistance to antibiotics, and promoter –511 polymorphism of the proinflammatory cytokine interleukin-1β (IL-1β). IL-1β is important in initiating the inflammatory response to Hp. In one study, the eradication rate was highest in patients with the IL-1β–511T/T genotype and lowest in the –511C/C genotype; heterozygous patients had intermediate eradication rates (42).

The impact of the *CYP2C19* genotype on cure rates for gastroesophageal reflux disease has been studied only in Japanese patients in two small trials (43, 44). The highest cure rates were observed in PMs (84.6% and 100%). Rates for hetEMs were 67.9% and 95%, and for EMs, 45.8% and 77.4%. PMs and hetEMs had 20% more therapeutic success against Hp than EMs. Based on these studies, clinical outcome may be improved by genotyping and giving EM patients a two- to fourfold higher dose of PPIs. However, prospective clinical trials are needed to prove that this approach improves clinical outcome and is cost-effective.

CYP2D6 and Antidepressant Therapy

More than 51 different major polymorphic *CYP2D6* alleles are known. Those most common in various ethnic groups are listed in Table 1. The variant *CYP2D6* alleles are classified on the basis of the enzyme's abolished, decreased, normal, increased, or qualitatively altered catalytic activity. Among the most important variants are *CYP2D6*2*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*10*, *CYP2D6*17*, and *CYP2D6*41*. There are also alleles carrying 2–13 active gene copies, which cause ultrarapid metabolism (45, 46).

Approximately 20%–25% of all drugs in clinical use are metabolized at least partly by CYP2D6 (46). Subjects with multiple active gene copies metabolize drugs more rapidly, whereas individuals lacking functional *CYP2D6* genes metabolize some CYP2D6 substrates at a lower rate and have a higher risk of ADRs. Adverse effects due to elevated drug plasma concentrations occur more often in PMs, in whom drug clearance depends mostly on CYP2D6 (see Reference 46).

In Western Europe, the incidence of PMs is ~7%. Ultrarapid metabolizers (UMs) are preferentially distributed in the Mediterranean area, where 10% of the population in Portugal, Spain, and Italy carries alleles with multiple *CYP2D6* gene copies (17, 46). Northern Europe has only ~1%–2% UMs, but as much as 5.5% of the Western European population consists of UMs who carry >2 active *CYP2D6* gene copies. An estimated 25 million people in Western Europe are PMs and are

TABLE 1 Major human polymorphic variant *CYP2D6* alleles and their global distribution

Major variant allele*	Mutation	Consequence	Allele frequency (%)			
			Caucasians	Asians	Black Africans	Ethiopians and Saudi Arabians
*CYP2D6*2xn*	Gene duplication/ multiduplication	Increased enzyme activity	1–5	0–2	2	10–16
*CYP2D6*4*	Defective splicing	Inactive enzyme	12–21	1	2	1–4
*CYP2D6*5*	Gene deletion	No enzyme	2–7	6	4	1–3
*CYP2D6*10*	P34S, S486T	Unstable enzyme	1–2	51	6	3–9
*CYP2D6*17*	T107I, R296C, S486T	Altered affinity for substrates	0	0	20–35	3–9

* All variant alleles are listed by the Human *CYP* Allele Nomenclature Committee at http://www.imm.ki.se/cypalleles/cyp2d6.htm.

often prescribed doses that are too high, whereas 20 million UMs are at risk of no response to drug treatment (16).

CYP2D6 metabolizes most tricyclic antidepressants (e.g., imipramine, nortriptyline, maprotiline, and others), whereas the metabolism of selective serotonin reuptake inhibitors depends mainly on CYP2C19. However, fluoxetine and paroxetine pharmacokinetics have been correlated with *CYP2D6* genotype (47).

A meta-analysis of the quantitative contribution of CYP2D6 polymorphism to the interindividual variation in dosage of antidepressants (48) has shown that the metabolism and dosage of imipramine, doxepin, maprotiline, trimipramine, desipramine, nortriptyline, clomipramine, and, partially, paroxetine depend on the CYP2D6 pheno- and genotype. Pharmacokinetic data suggest dose adjustments for these drugs that range from 28% to 60% of the normal dose for PMs and 180% to 140% of normal dosage for UMs. In general, based on the impact of CYP2D6 on dosage adaptation of antidepressants and antipsychotics, 40%–50% of drugs may be subject to important pharmacokinetic alterations owing to CYP2D6 polymorphism. This figure extrapolates to ∼10%–12% of all clinically used drugs.

An interesting relationship exists between nonresponders to antidepressant therapy and the UM phenotype. Initial studies (49) revealed that the number of active *CYP2D6* gene copies had a strong impact on the pharmacokinetics of nortriptyline. Later, two independent studies indicated a 5–10-fold higher than expected incidence of UMs among nonresponders (50, 51). This finding implies that nonresponse to antidepressant therapy due to ultrarapid metabolism of the drug is an important clinical issue and that a higher response rate could be obtained in a significant fraction of Europeans if dosing were based on the CYP2D6 pheno/genotype.

Further prospective studies are needed to define the cost-benefit ratio of pharmacogenetic individualization of therapy with these and other CYP2D6 substrates.

TPMT and Thiopurine Therapy

TPMT catalyzes the S-methylation (inactivation) of the thiopurine drugs mercaptopurine, azathioprine, and thioguanine (52, 53). These agents are commonly used to treat leukemia, rheumatic diseases, inflammatory bowel diseases, and solid organ transplantation. In hematopoietic tissues, TPMT is the predominant inactivation pathway, so patients who inherit TPMT deficiency accumulate excessive levels of active thioguanine nucleotides after receiving standard doses. Genetic polymorphism of TPMT affects its activity: Approximately 90% of individuals inherit high activity, 10% intermediate activity due to heterozygosity, and 0.3% low or no detectable activity because of two nonfunctional TPMT alleles (Figure 2) (54, 55). Numerous studies have shown that TPMT-deficient patients are at high risk of severe, sometimes fatal, hematologic toxicity (56–58); TPMT heterozygotes have an intermediate risk of hematologic toxicity (59, 60). Patients who inherit two nonfunctional variant alleles should be given 6%–10% of the standard dose of thiopurines (Figure 2), whereas heterozygous patients can usually start on full doses but are significantly more likely to require dose reduction to avoid toxicity. TPMT deficiency has also been associated with a high risk of irradiation-induced brain tumors in patients given thiopurines concomitantly with radiation therapy (61).

Three variant alleles (*TPMT*2*, *TPMT*3A*, and *TPMT*3C*) account for TPMT deficiency in >95% of patients (54, 55, 62, 63), and reference laboratories now offer TPMT genotyping as a Clinical Laboratory Improvement Amendments–certified molecular diagnostic. More than 98% concordance exists between TPMT genotype and phenotype, and genotyping is highly sensitive (90%) and specific (99%) in identifying patients who have inherited one or two nonfunctional TPMT alleles, so it is a reliable method for guiding thiopurine therapy (64). Furthermore, outcome of acute lymphoblastic leukemia (ALL) in children is related to mercaptopurine dose intensity: Better event-free survival or early treatment response was observed in children with intermediate or low TPMT activity than in those of homozygous wild-type phenotype (65, 66). These results indicate that increasing mercaptopurine doses in children with wild-type TPMT may improve treatment outcome. In a recent study in which mercaptopurine doses were adjusted based on TPMT status, the efficacy of childhood ALL therapy was influenced by glutathione-S-transferase M1 and thymidylate synthetase genotypes (67).

Irinotecan and Uridine Diphospho Glucuronosyl Transferase 1A1 (UGT1A1)

Irinotecan is now being used to treat several human cancers, including colon and lung cancer in adults and pediatric solid tumors such as rhabdomyosarcoma and

neuroblastoma. It must be activated by carboxylesterase to 7-ethyl-10-hydroxy-camptothecin, which inhibits topoisomerase I. UGT1A1 catalyzes the conjugation of glucuronide to SN-38; the conjugated metabolite is relatively inactive and more readily eliminated in bile and urine. The dose-limiting toxicities of irinotecan, diarrhea and leukopenia (68), are associated with higher levels of SN-38. Because *UGT1A1* expression differs widely among patients, and studies have shown up to 50-fold interpatient differences in the rate of SN-38 glucuronidation (69, 70), the clinical pharmacological effects of irinotecan have been associated with the extent of SN-38 glucuronidation.

UGT1A1 is a member of a large gene family of up to 12 UGT-glucuronosyltransferases encoded by the human *UGT1* locus. Reduced expression of *UGT1A1*, which is associated with increased blood concentrations of unconjugated bilirubin, may be linked to polymorphism in the *UGT1A* coding region (Crigler-Najjar syndromes) or differences in the number of TA repeats in the *UGT1A1* promoter region (Gilbert's syndrome). In patients with Gilbert's syndrome, who generally have six TA repeats, reduced glucuronidation is associated with seven TA repeats, homozygosity for which (*UGT1A1*28*) occurs in 12%–16% of patients (68, 69). SN-38 glucuronidation is correlated with the number of TA repeats (69, 70). Patients homozygous or heterozygous for seven TA repeats have a sevenfold higher likelihood of diarrhea and/or leukopenia with irinotecan therapy than do patients with the wild-type genotype (six TA repeats) (68, 69, 71).

Interpatient differences in irinotecan metabolism are also linked to polymorphism of carboxylesterase (72, 73) and, possibly, *CYP3A4* (74) and *CYP3A5*. Also, the expression and function of UGT1A1 may be influenced by the presence, in its promoter, of a DNA recognition/binding site for the nuclear receptor CAR (constitutive activated receptor), a phenobarbital response element (75).

DRUG TRANSPORT

Until recently, absorption of drugs from the gastrointestinal tract was considered to be a largely passive process depending on crystal size, solubility, lipophilicity, pKa of the drug, and pH of the intestinal fluid. Transfer of the absorbed drug into tissues was thought to depend on the drug's physicochemical properties and protein binding ability.

It is now known that many drugs are substrates of active transporters, membrane proteins that maintain cellular homeostasis by importing and exporting endogenous compounds. Because of their localization in intestinal, hepatic, and renal epithelial cells, these transporters are important in the absorption, bioavailability, and elimination of many drugs. Moreover, they can be important in targeting drugs to organs because they are localized in blood-organ barriers. Genetic polymorphisms affecting their expression or changing their affinity for substrates can alter the absorption and elimination of drugs that are their substrates, and can alter drug concentrations at the site of action despite similar blood concentrations.

MDR1, MRPs, OATPs, OCTs, OATs, and nucleoside transporters are of particular interest because they transport exogenous substrates, including drugs, as well as endogenous compounds.

P-glycoprotein (Pgp), the product of *ABCB1* (alias *MDR1*, for "multidrug resistance"), has received much attention because its substrates include many important drugs. Studies on *mdr1a*-deficient mice (76) provided convincing evidence that Pgp plays a prominent role in the blood-tissue barrier. Pgp-knockout mice had brain concentrations of cardiac glycosides, HIV-1 protease inhibitors, and immunosuppressants up to 50 times higher than those in wild-type animals.

Systemic screening initially revealed 15 genetic variants of human *ABCB1*. A total of 28 SNPs have now been identified; those in exons 21 (G2677T) and 26 (C3435T) are of particular interest because they affect expression or function (77, 78). Although several studies have addressed the association of these variants with disposition and effects of Pgp substrates, controversy remains about the influence of different variants on pharmacokinetics and pharmacodynamics.

Tissues studied so far have shown an average eight- to tenfold difference in Pgp expression. The 3435CC and 3435TT genotypes show a two- to threefold difference in Pgp expression in duodenum, kidney, peripheral leukocytes, and placenta, with substantial overlap between genotypes. This modest difference suggests a moderate impact of the *ABCB1* genotypes on the disposition and effects of Pgp substrates; nongenetic factors probably play an important role in modifying Pgp expression. Differences of ~25%–35% in the bioavailability and renal clearance of digoxin in relation to the exon 21 or exon 26 SNP have been reported (79–82).

Several studies have addressed the relevance of *ABCB1* polymorphism to dose requirements, blood concentrations, chronic rejection, and chronic nephrotoxicity in renal transplant patients receiving the calcineurin inhibitors cyclosporine A and tacrolimus. Animal studies have linked low expression of Pgp in renal tissue with chronic cyclosporine nephrotoxicity. Published data on other Pgp substrates are controversial; no significant differences were observed for any of the parameters investigated (83–85). These studies, however, did not consider discordance in the genotypes of the organ recipient and donor. Indeed, the *ABCB1* genotype of the donor, but not the recipient, may be a major risk factor for cyclosporine-related chronic nephrotoxicity in recipients of renal transplants (86). The *ABCB1* 3435TT genotype, which is associated with lower Pgp expression in renal parenchymal cells, is strongly associated with cyclosporine nephrotoxicity (odds ratio 13.4) (86).

Because all currently used HIV protease inhibitors are Pgp substrates, studies have focused on whether differences in the expression of Pgp could explain some of the variability observed in CD4 cell recovery (87–90). CD4 cells are a major target of HIV. Variability of Pgp expression in CD4 subpopulations may affect intracellular concentrations of HIV protease inhibitors and antiretroviral efficacy. Indeed, a recent study showed that six months after antiretroviral therapy began, a significantly greater increase in CD4 cell count and a more pronounced decrease

in viral load occurred in patients with the 3435TT genotype than in those with the 3435CT or CC genotype (91), but these findings have not been confirmed by others.

Pgp expressed on the luminal side of endothelial cells of the brain capillaries drastically limits the transfer of many drugs from blood to brain, as evidenced by a huge increase in brain-to-blood concentration in mdr1a-knockout mouse. Because many CNS-active drugs are Pgp substrates, differences in *ABCB1* expression at the blood-brain barrier could help explain why patients with identical plasma concentrations respond differently and have different side effects. In a recent study, 25% of patients with the TT, 13.7% with the CT, and none with the CC genotype developed nortriptyline-induced postural hypotension, even though all patients had received similar doses of nortriptyline and had similar nortriptyline plasma levels (92).

The consequences of genetic polymorphism have been assessed in vivo for only one other transporter of relevance for drug therapy, OATP-C (SCP1B1), which facilitates the uptake of drug substrates from the blood into the hepatocyte. The relatively common variant OATP-C*5 is associated with markedly reduced transporter function (93). Carriers of the *5 allele have high plasma concentrations of the OATP-C substrate pravastatin (94–96), suggesting impaired uptake of pravastatin by hepatocytes. Indeed, pravastatin concentrations in hepatocytes are low, which results in less inhibition of cholesterol synthesis as assessed by decreased lathosterol concentration and lathosterol/cholesterol ratio (97). Whether cholesterol-lowering efficacy is impaired in carriers of these variants during long-term treatment is yet unknown.

A profound impact of OATP-C polymorphism was recently demonstrated for the antidiabetic drug repaglinide, for which AUCs were approximately three times higher in carriers of the variant *5 allele than in wild-type subjects. This effect was associated with a more pronounced reduction of blood glucose levels (98).

RECEPTORS

A growing number of drug targets (e.g., receptors) are known to exhibit genetic polymorphisms that influence drug response in humans (1, 2, 99). Here we use the β_2-adrenergic receptor and the sodium channel SCN1A to illustrate the potential importance of inherited differences in drug targets in drug response.

β_2 Adrenergic Receptor (ADRB2)

Genetic polymorphism of the β_2-adrenoreceptor (ADBR2), which interacts with endogenous catecholamines and various medications, can alter the effects of medications that target it (100–102). A number of distinct SNPs are associated with altered expression, downregulation, or coupling of ADBR2 (94). SNPs resulting in amino acid alterations of Arg to Gly at codon 16 and Gln to Glu at codon

27 are relatively common (allele frequency 0.4–0.65); their clinical relevance is under intensive investigation. Patients homozygous for *ADBR2* codon 16 Arg are reported to have near-complete desensitization after continuous infusion of isoproterenol, with venodilatation decreasing from 44% at baseline to 8% at 90 min of infusion. In contrast, there was no significant change in venodilatation in patients homozygous for Gly at codon 16, regardless of their codon 27 genotype. Maximal venodilatation in response to isoproterenol was higher in patients homozygous for Glu at codon 27 than in patients with Gln at codon 27, regardless of codon 16 status (95).

These findings are largely consistent with studies showing that FEV_1 response to a single dose of oral albuterol was higher (6.5-fold) in patients with a *ADBR2* codon 16 Arg/Arg genotype than in Gly/Gly patients (103). The genotype effect differed with chronic inhaled β-agonist therapy; morning peak expiratory flow (AM-PEF) gradually declined in patients with the Arg/Arg genotype but did not change in patients with the Gly/Gly genotype (104). AM-PEF decreased dramatically after cessation of inhaled β-agonist therapy in Arg/Arg but not in Gly/Gly patients (104). Patients with the Arg/Arg genotype who receive regularly scheduled inhaled β-agonists may therefore be at risk of deleterious effects and may require alternative schedules and/or earlier anti-inflammatory treatment. These findings are consistent with the desensitization of ADBR2 in patients with a codon 16 Arg/Arg genotype (102).

At least 13 distinct SNPs have so far been identified in *ADBR2* (105). This has prompted evaluation of the importance of haplotype structure instead of individual SNPs in determining receptor function and pharmacological response. Of the 8192 possible *ADBR2* haplotypes, only 12 were observed among 77 white, black, Asian, and Hispanic/Latino subjects (105). Assessment of β-agonist therapy in asthma patients revealed a better association of bronchodilator response with haplotype than with any SNP alone (105). This is not surprising, as haplotype structure often predicts phenotypic consequences better than do SNPs (106).

Variants of the ADRB2, ADRB1, and other G-protein coupled receptors (GPCRs) generally encode hypomorphic proteins, not nonfunctional proteins (3, 99). This fact may be related to the essential functions of the GPCRs, the absence of which is incompatible with life or, at least, strongly selected against. Note also that not all clinical studies of ADRB1/2 polymorphisms have yielded concordant pharmacogenetic findings (3, 99), which may reflect differences in the patient populations studied, the drug response phenotypes measured, and/or the way in which medications were given or other confounding variables (e.g., other genetic polymorphisms).

The SCN1 Sodium Channel

The HapMap project is rapidly providing important new insights into the presence and evolution of various haplotype blocks in the human genome (see http://www.hapmap.org/index.html.en). With the possibility that tagging SNPs reduce the

number of SNPs indicative of various haplotype blocks (107), genotyping for various receptor haplotypes may become more feasible. Such an approach identified an intronic polymorphism of the SCN1 sodium channel that alters splicing of the receptor and is related to the dosage required by epileptic patients receiving carbamazepine (108). This efficient way of identifying haplotype blocks and SNP markers may facilitate more rapid determination of haplotype receptor variations that influence drug response.

THE WAY FORWARD

Most of the genetic polymorphisms characterized to date that influence drug response in humans are highly penetrant monogenic traits: Inherited difference in a single gene has such a profound effect on the pharmacokinetics or pharmacodynamics of a drug that interindividual difference in one gene has a clinically important effect on drug response. These are the "low-hanging fruit" of pharmacogenetics. However, the effects of most drugs are determined by many proteins, and composite genetic polymorphisms in multiple genes coupled with nongenetic factors will be found to determine drug response. New strategies are therefore needed to identify, for a given drug, the relevant genes and genetic polymorphisms and the pathways and processes in their interaction. The various strategies now being used include genome-wide haplotype mapping (1), gene expression analyses (109, 110), and proteomic methods, as well as "candidate gene" approaches based on known pharmacokinetic (111) and pharmacodynamic (67) factors. These approaches, with evolving statistical and biological (pathway) models and quantitative genotyping in some target tissues (112), are likely to be critical for studies that aim to elucidate polygenic determinants of drug response. Clinical validation of these polygenic models will require large clinical trials of uniformly treated and systematically characterized patients, high-throughput genomic methods, and sophisticated bioinformatics analyses. Such studies hold great promise to yield a new panel of molecular diagnostics (i.e., genotypes) that can be used to improve drug therapy by reducing toxicity and increasing efficacy.

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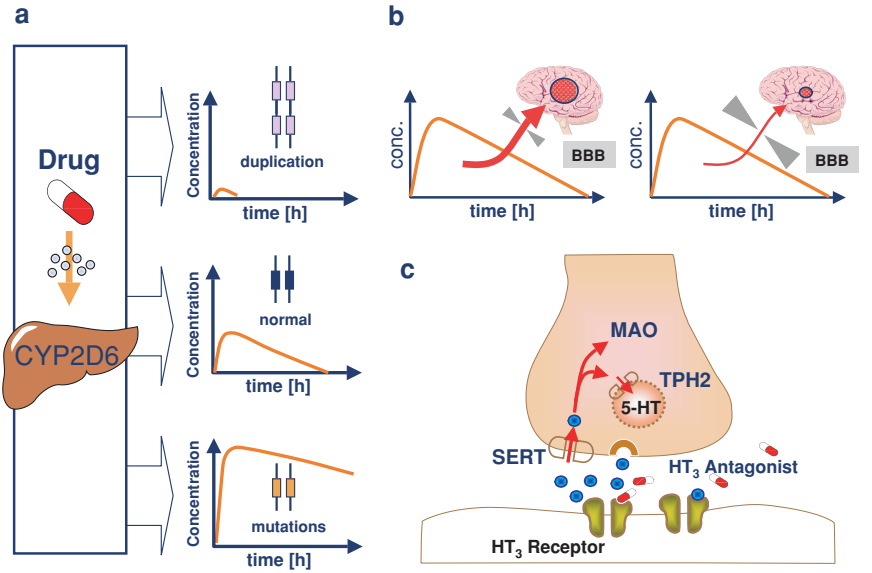

Figure 1 Drug-response phenotype is a complex trait. (*a*) The HT_3 antagonist tropisetrone is a CYP2D6 substrate. After receiving the same dose, patients with high enzyme activity due to gene duplication will not achieve effective drug concentrations. (*b*) Because the drug is a Pgp substrate, transfer from blood to central nervous system will be influenced by the level of Pgp expression, an additional source of variability, at the blood-brain barrier (BBB). (*c*) The magnitude of response at the HT_3 receptor is influenced not only by drug concentration but also by genetic polymorphisms in the receptor and concentration of neutrotransmitter in the synaptic cleft. Serotonin concentration is influenced by proteins involved in biosynthesis (TPH2, tryptophane hydroxylase 2), transport (SERT, high-affinity serotonin reuptake transporter), and catabolism (MAO, monoamine oxidase). Genetic polymorphisms that affect function have been described for all of the genes encoding these proteins. A pharmacogenetic analysis of nonresponse or poor response (observed in ~30% of patients) should include all of these candidate genes.

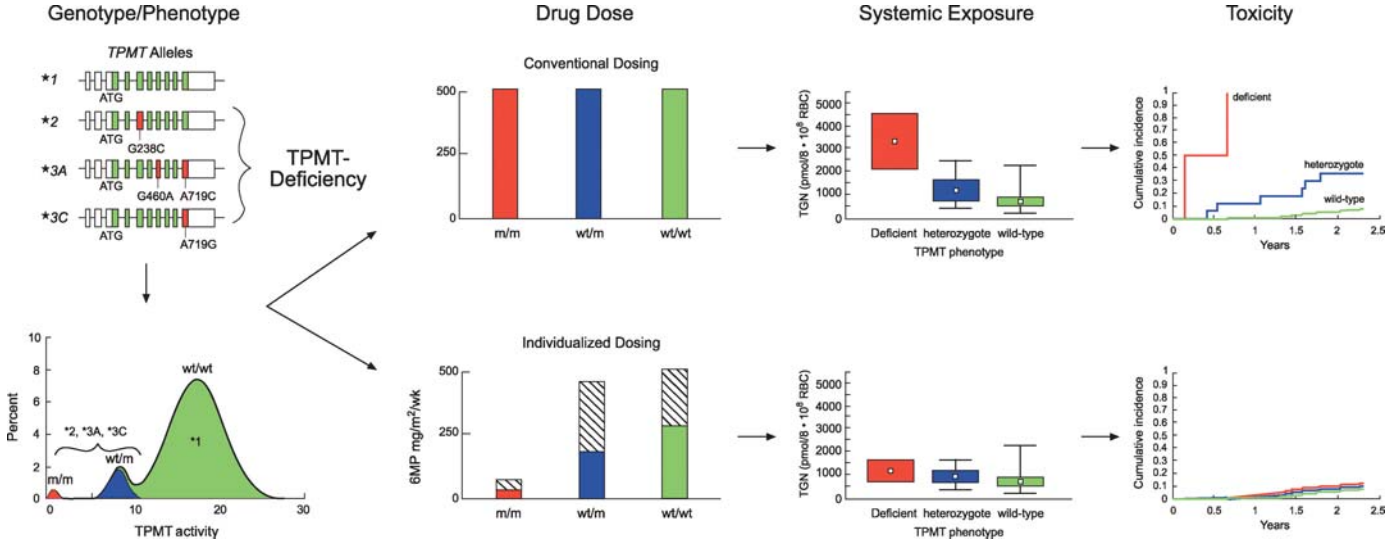

Figure 2 Genetic polymorphism of thiopurine S-methyltransferase (TPMT) and its role in determining response to thiopurine medications (azathioprine, mercaptopurine, thioguanine). The far left panels depict the predominant TPMT mutant alleles causing autosomal codominant inheritance of TPMT activity in humans. As depicted in the adjacent top three panels, when uniform (conventional) dosages of thiopurine medications are given to all patients, TPMT-deficient patients accumulate tenfold higher cellular concentrations of the active thioguanine nucleotides (TGN), and heterozygous patients accumulate about twofold higher TGN concentrations. These differences translate into a significantly higher frequency of toxicity (*far right panels*). As depicted in the bottom three panels, when genotype-specific dosing is used [colored bars depict mercaptopurine (6MP) doses that were tolerated in patients who presented with hematopoietic toxicity (59)], similar cellular TGN concentrations are achieved, and all three TPMT phenotypes can be treated without acute toxicity.

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