REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects

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It is well recognized that different patients respond in different ways to the same medication. These differences are often greater among members of a population than they are within the same person at different times (or between monozygotic twins).[1] The existence of large population differences with small intrapatient variability is consistent with inheritance as a determinant of drug response; it is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects.[2] Although many nongenetic factors influence the effects of medications, including age, organ function, concomitant therapy, drug interactions, and the nature of the disease, there are now numerous examples of cases in which interindividual differences in drug response are due to sequence variants in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets.[3-5] Unlike other factors influencing drug response, inherited determinants generally remain stable throughout a person's lifetime.

Clinical observations of inherited differences in drug effects were first documented in the 1950s,[6-9] giving rise to the field of pharmacogenetics, and later pharmacogenomics. Although the two terms are synonymous for all practical purposes, pharmacogenomics uses genome-wide approaches to elucidate the inherited basis of differences between persons in the response to drugs.

More than 1.4 million single-nucleotide polymorphisms were identified in the initial sequencing of the human genome,[10] with over 60,000 of them in the coding region of genes. Some of these single-nucleotide polymorphisms have already been associated with substantial changes in the metabolism or effects of medications, and some are now being used to predict clinical response.[3-5,11] Because most drug effects are determined by the interplay of several gene products that influence the pharmacokinetics and pharmacodynamics of medications, including inherited differences in drug targets (e.g., receptors) and drug disposition (e.g., metabolizing enzymes and transporters), polygenic determinants of drug effects (Fig. 1) have become increasingly important in pharmacogenomics. In this review, we focus on the therapeutic consequences of inherited differences in drug disposition and drug targets. An accompanying review[12] focuses on the pharmacogenetics of drug metabolism. This review is not meant to be exhaustive; rather, clinically relevant examples are used to illustrate how pharmacogenomics can provide molecular diagnostic methods that improve drug therapy.

Genetic Polymorphisms Influencing Drug Disposition

The field of pharmacogenetics began with a focus on drug metabolism,[12] but it has been extended to encompass the full spectrum of drug disposition, including a growing list of transporters that influence drug absorption, distribution, and excretion.[3-5,13]

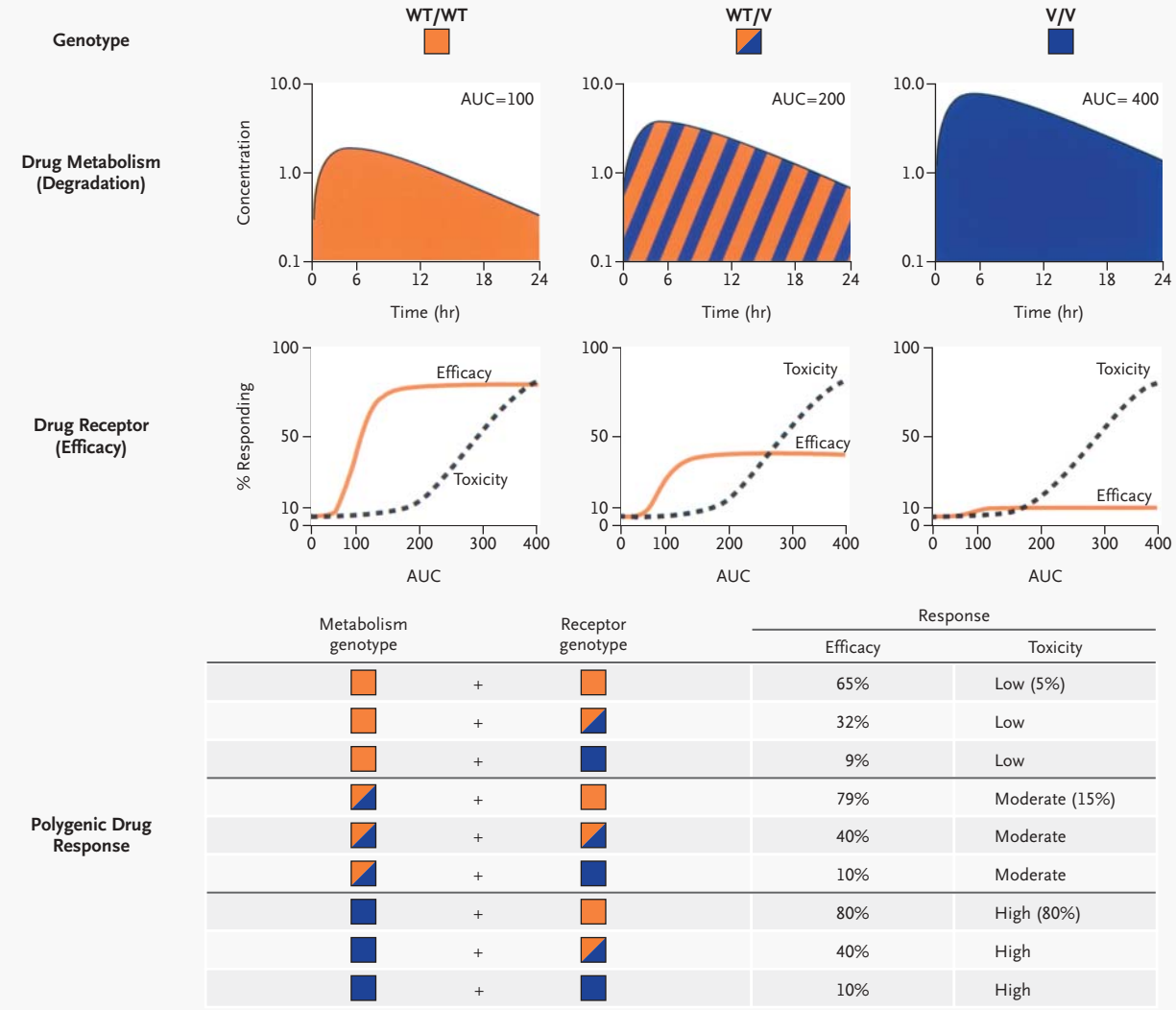


Figure 1. Polygenic Determinants of Drug Response.

The potential effects of two genetic polymorphisms are illustrated, one involving a drug-metabolizing enzyme (top) and the second involving a drug receptor (middle), depicting differences in drug clearance (or the area under the plasma concentration–time curve [AUC]) and receptor sensitivity in patients who are homozygous for the wild-type allele (WT/WT), are heterozygous for one wild-type and one variant (V) allele (WT/V), or have two variant alleles (V/V) for the two polymorphisms. At the bottom are shown the nine potential combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data at the top, yielding therapeutic indexes (efficacy:toxicity ratios) ranging from 13 (65 percent:5 percent) to 0.125 (10 percent:80 percent).

DRUG METABOLISM

There are more than 30 families of drug-metabolizing enzymes in humans,[3,14] and essentially all have genetic variants, many of which translate into functional changes in the proteins encoded. These monogenic traits are discussed by Weinshilboum.[12] But there is an instructive example of a multigenic effect involving the CYP3A family of P-450 enzymes. About three quarters of whites and half of blacks have a genetic inability to express functional CYP3A5.[15] The lack of functional CYP3A5 may not be readily evident, because many medications metabolized by CYP3A5 are also metabolized by the universally expressed CYP3A4. For medications that are equally metabolized by both enzymes, the net rate of metabolism is the sum of that due to CYP3A4 and that due to CYP3A5; the existence of this dual pathway partially obscures the clinical effects of ge-

netic polymorphism of CYP3A5 but contributes to the large range of total CYP3A activity in humans (Fig. 2). The CYP3A pathway of drug elimination is further confounded by the presence of single-nucleotide polymorphisms in the *CYP3A4* gene that alter the activity of this enzyme for some substrates but not for others.[16] The genetic basis of CYP3A5 deficiency is predominantly a single-nucleotide polymorphism in intron 3 that creates a cryptic splice site causing 131 nucleotides of the intronic sequence to be inserted into the RNA, introducing a termination codon that prematurely truncates the CYP3A5 protein.[15] Although it is now possible to determine which patients express both functional enzymes (i.e., CYP3A4 and CYP3A5), the clinical importance of these variants for the many drugs metabolized by CYP3A remains unclear.

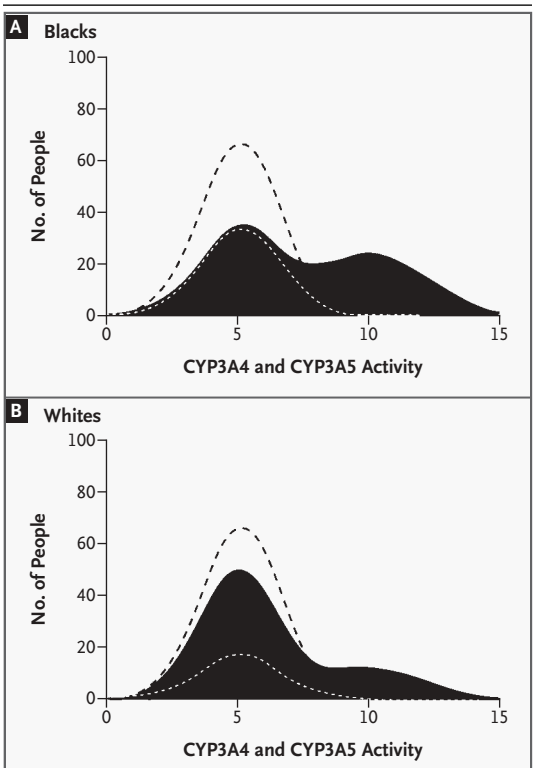


Figure 2. Simulated Activities of Cytochromes P-450 CYP3A4 and CYP3A5 in Blacks and Whites.

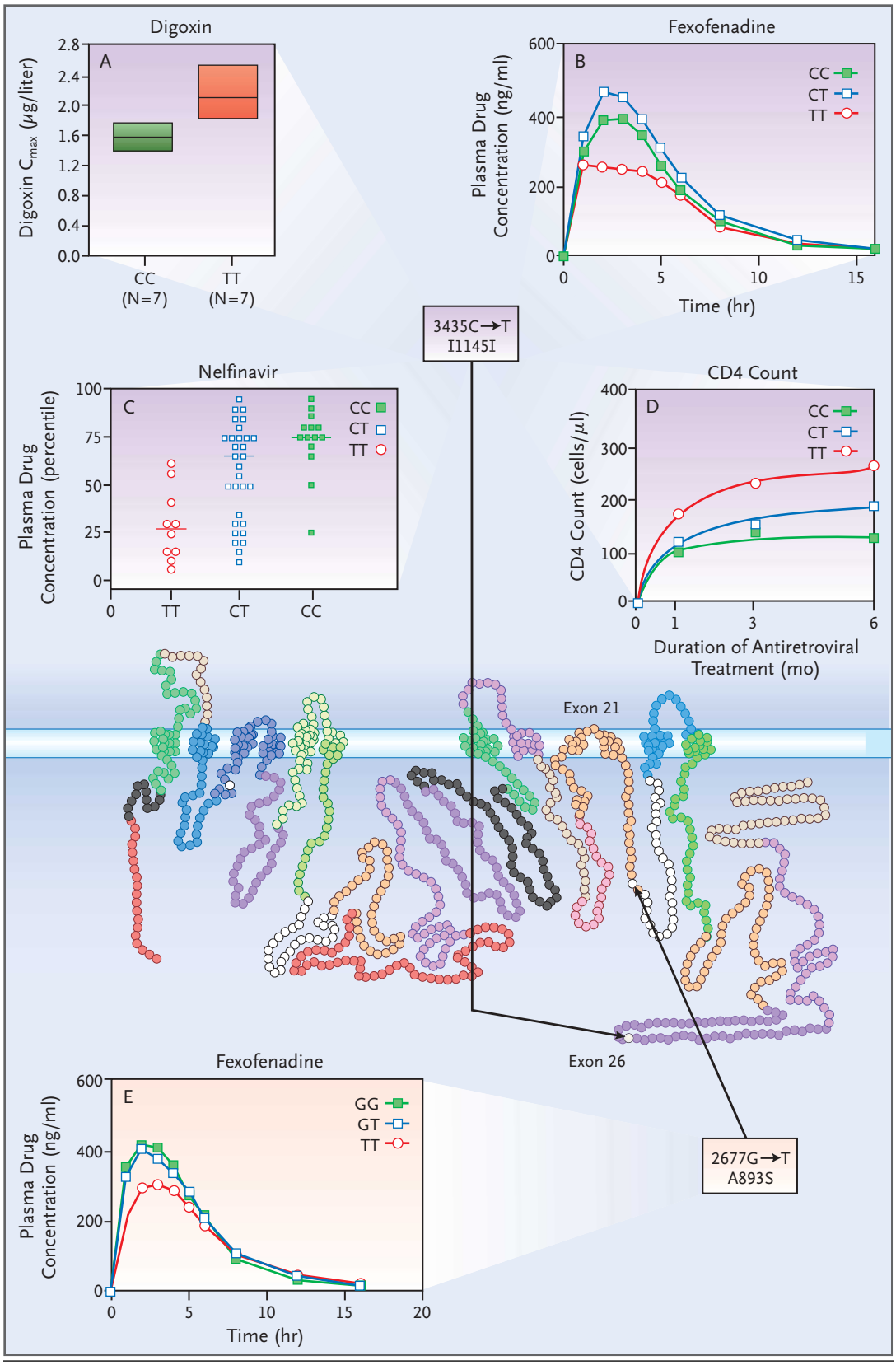
The simulated activities of CYP3A4 (black dashed lines) and CYP3A5 (white dashed lines) are shown in blacks (Panel A) and whites (Panel B), assuming a normal distribution and a 10-fold range in activity (shown in arbitrary units) among those expressing functional forms of these enzymes, and further assuming that all patients express CYP3A4, but that only 25 percent of whites and 50 percent of blacks express functional CYP3A5 because of genetic polymorphism. The solid area reflects the combined activity of CYP3A4 and CYP3A5 in the two populations for medications that are metabolized equally by the two enzymes.

DRUG TRANSPORTERS

Transport proteins have an important role in regulating the absorption, distribution, and excretion of many medications. Members of the adenosine triphosphate (ATP)–binding cassette family of membrane transporters[17] are among the most extensively studied transporters involved in drug disposition and effects. A member of the ATP-binding cassette family, P-glycoprotein, is encoded by the human *ABCB1* gene (also called *MDR1*). A principal function of P-glycoprotein is the energy-dependent cellular efflux of substrates, including bilirubin, several anticancer drugs, cardiac glycosides, immunosuppressive agents, glucocorticoids, human immunodeficiency virus (HIV) type 1 protease inhibitors, and many other medications (Fig. 3).[17,21,22] The expression of P-glycoprotein in many normal tissues suggests that it has a role in the excretion of xenobiotics and metabolites into urine, bile, and the intestinal lumen.[23,24] At the blood–brain barrier, P-glycoprotein in the choroid plexus limits the accumula-

Figure 3 (facing page). Functional Consequences of Genetic Polymorphisms in the Human P-Glycoprotein Transporter Gene *ABCB1* (or *MDR1*).

The schematic diagram of the human P-glycoprotein was adapted from Kim et al.,[18] with each circle representing an amino acid and each color a different exon encoding the corresponding amino acids. Two single-nucleotide polymorphisms in the human *ABCB1* gene have been associated with altered drug disposition (Panels A, B, C, and E) or altered drug effects (Panel D). The synonymous single-nucleotide polymorphism (a single-nucleotide polymorphism that does not alter the amino acid encoded) in exon 26 (the 3435C→T single-nucleotide polymorphism) has been associated with higher oral bioavailability of digoxin in patients homozygous for the T nucleotide (Panel A [C_{max} denotes maximal concentration])[19] but lower plasma concentrations after oral doses of fexofenadine (Panel B)[18] and nelfinavir (Panel C).[20] This single-nucleotide polymorphism has also been linked to better CD4 cell recovery in HIV-infected patients who are treated with nelfinavir and other antiretroviral agents (Panel D).[20] The single-nucleotide polymorphism at nucleotide 2677 (G→T) has been associated with lower plasma fexofenadine concentrations in patients homozygous for the T nucleotide at position 2677 (Panel E).[18] The panels have been adapted from Kim et al.,[18] Hoffmeyer et al.,[19] and Fellay et al.[20]



tion of many drugs in the brain, including digoxin, ivermectin, vinblastine, dexamethasone, cyclosporine, domperidone, and loperamide.[23-25] A synonymous single-nucleotide polymorphism (i.e., a single-nucleotide polymorphism that does not alter the amino acid encoded) in exon 26 (3435C→T) has been associated with variable expression of P-glycoprotein in the duodenum; in patients homozygous for the T allele, duodenal expression of P-glycoprotein was less than half that in patients with the CC genotype.[19] CD56+ natural killer cells from subjects homozygous for 3435C demonstrated significantly lower ex vivo retention of the P-glycoprotein substrate rhodamine (i.e., higher P-glycoprotein function).[26] Digoxin, another P-glycoprotein substrate, has significantly higher bioavailability in subjects with the 3435TT genotype.[19,27] As is typical for many pharmacogenetic traits, there is considerable racial variation in the frequency of the 3435C→T single-nucleotide polymorphism.[28-30]

The 3435C→T single-nucleotide polymorphism is in linkage disequilibrium with a nonsynonymous single-nucleotide polymorphism (i.e., one causing an amino acid change) in exon 21 (2677G→T, leading to Ala893Ser) that alters P-glycoprotein function.[18] Because these two single-nucleotide polymorphisms travel together, it is unclear whether the 3435C→T polymorphism is of functional importance or is simply linked with the causative polymorphism in exon 21. The 2677G→T single-nucleotide polymorphism has been associated with enhanced P-glycoprotein function in vitro and lower plasma fexofenadine concentrations in humans,[18] effects opposite to those reported with digoxin.[27]

The associations between treatment outcome and genetic variants in *CYP3A4*, *CYP3A5*, *CYP2D6*, *CYP2C19*, the chemokine receptor gene *CCR5*, and *ABCB1* have been examined in HIV-infected patients receiving combination antiretroviral therapy with either a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor.[20] The *ABCB1* 3435C→T polymorphism was associated with significant differences in the plasma pharmacokinetics of nelfinavir (Fig. 3) and efavirenz. Recovery of the CD4 cell count was significantly greater and more rapid in patients with the TT genotype than in patients with either the CT or the CC genotype (Fig. 3). Of many variables evaluated, only the *ABCB1* genotype and the base-line number of HIV RNA copies were significant predictors of CD4 recovery.[20] However, the *ABCB1* 2677G→T single-nucleotide polymorphism was not genotyped, so it remains unclear whether the 3435C→T polymorphism is causative or is simply linked with another polymorphism that is causative.

This example illustrates a common problem in association studies, namely, biologic plausibility. It is not obvious how greater efficacy (CD4 recovery) could be linked to a single-nucleotide polymorphism associated with lower plasma drug concentrations, unless there are specific effects of the *ABCB1* polymorphisms that cause decreased drug efflux from CD4 leukocytes. Overexpression of the gene for another ABC transporter (*ABCC4*, or *MRP4*) confers resistance to some nucleoside antiretroviral agents (e.g., zidovudine).[31] Despite the uncertainty about the mechanisms involved, the clinical value is that a host genetic marker can predict immune recovery after the initiation of antiretroviral treatment and, if validated, may offer a new strategy in tailoring HIV therapy.

GENETIC POLYMORPHISM OF DRUG TARGETS

Genetic variation in drug targets (e.g., receptors) can have a profound effect on drug efficacy, with over 25 examples already identified (Table 1).[3-5] Sequence variants with a direct effect on response occur in the gene for the β_2-adrenoreceptor, affecting the response to β_2-agonists[43,44]; arachidonate 5-lipoxygenase (ALOX5), affecting the response to ALOX5 inhibitors[42]; and angiotensin-converting enzyme (ACE), affecting the renoprotective actions of ACE inhibitors.[32] Genetic differences may also have indirect effects on drug response that are unrelated to drug metabolism or transport, such as methylation of the methylguanine methyltransferase (MGMT) gene promoter, which alters the response of gliomas to treatment with carmustine.[63] The mechanism of this effect is related to a decrease in the efficiency of repair of alkylated DNA in patients with methylated MGMT. It is critical to distinguish this target mechanism from genetic polymorphisms in drug-metabolizing enzymes that affect response by altering drug concentrations, such as the thiopurine methyltransferase polymorphism associated with the hematopoietic toxicity of mercaptopurine[64-66] and susceptibility to radiation-induced brain tumors.[67]

The β_2-adrenoreceptor (coded by the *ADRB2* gene) illustrates another link between genetic polymorphisms in drug targets and clinical responses. Genetic polymorphism of the β_2-adrenoreceptor can alter the process of signal transduction by these receptors.[43,44] Three single-nucleotide polymor-

Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.*

Gene or Gene Product	Medication	Drug Effect Associated with Polymorphism
ACE	ACE inhibitors (e.g., enalapril) Fluvastatin	Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function[32-40] Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis[41]
Arachidonate 5-lipoxygenase	Leukotriene inhibitors	Improvement in FEV_1[42]
β_2-Adrenergic receptor	β_2-Agonists (e.g., albuterol)	Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects[43-50]
Bradykinin B2 receptor	ACE inhibitors	ACE-inhibitor–induced cough[51]
Dopamine receptors (D2, D3, D4)	Antipsychotics (e.g. haloperidol, clozapine)	Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3)[52-56]
Estrogen receptor-α	Conjugated estrogens Hormone-replacement therapy	Increase in bone mineral density[57] Increase in high-density lipoprotein cholesterol[58]
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa	Aspirin or glycoprotein IIb/IIIa inhibitors	Antiplatelet effect[59]
Serotonin (5-hydroxytryptamine) transporter	Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)	5-Hydroxytryptamine neurotransmission, antidepressant response[60-62]

* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review. ACE denotes angiotensin-converting enzyme, and FEV_1 forced expiratory volume in one second.

phisms in *ADRB2* have been associated with altered expression, down-regulation, or coupling of the receptor in response to β_2-adrenoreceptor agonists.[43] Single-nucleotide polymorphisms resulting in an Arg-to-Gly amino acid change at codon 16 and a Gln-to-Glu change at codon 27 are relatively common, with allele frequencies of 0.4 to 0.6, and are under intensive investigation for their clinical relevance.

A recent study of agonist-mediated vasodilatation and desensitization[44] revealed that patients who were homozygous for Arg at *ADRB2* codon 16 had nearly complete desensitization after continuous infusion of isoproterenol, with venodilatation decreasing from 44 percent at base line to 8 percent after 90 minutes of infusion (Fig. 4). In contrast, patients homozygous for Gly at codon 16 had no significant change in venodilatation, regardless of their codon 27 status. Polymorphism at codon 27 was also of functional relevance; subjects homozygous for the Glu allele had higher maximal venodilatation in response to isoproterenol than those with the codon 27 Gln genotype, regardless of their codon 16 status (Fig. 4).[44]

These results are generally consistent with those of studies showing that the forced expiratory volume in one second (FEV_1) after a single oral dose of albuterol was higher by a factor of 6.5 in patients with the Arg/Arg genotype at codon 16 of *ADRB2* than in those with the Gly/Gly genotype (Fig. 4).[48] However, the influence of this genotype was different in patients receiving long-term, regularly scheduled therapy with inhaled β-agonists. Among these patients, those with the Arg/Arg genotype had a gradual decline in the morning peak expiratory flow measured before they had used medication, whereas no change was observed in patients with the Gly/Gly genotype.[47] In addition, the morning peak expiratory flow deteriorated dramatically after the cessation of therapy in patients with the Arg/Arg genotype, but not in those with the Gly/Gly genotype.[47] These data suggest that a codon 16 Arg/Arg genotype may identify patients at risk for deleterious or nonbeneficial effects of regularly scheduled therapy with inhaled β-agonists; the data also suggest that these patients may be candidates for alternative schedules of therapy, earlier initiation of anti-inflammatory agents, or both. These findings are also consistent with the aforementioned desensitization of the β_2-adrenoreceptor in patients with a codon 16 Arg/Arg genotype.[44]

At least 13 distinct single-nucleotide polymorphisms have been identified in *ADRB2*.[46] This finding has led to evaluation of the importance of hap-

lotype structure as compared with individual single-nucleotide polymorphisms in determining receptor function and pharmacologic response. Among 77 white, black, Asian, and Hispanic subjects, only 12 distinct haplotypes of the 8192 possible *ADRB2* haplotypes were actually observed.[46] The bronchodilator response to inhaled β-agonist therapy in patients with asthma revealed a stronger association between bronchodilator response and haplotype than between bronchodilator response and any single-nucleotide polymorphism alone.[46] This is not surprising, because haplotype structure is often a better predictor of phenotypic consequences than are individual polymorphisms. This result suggests that it would be desirable to develop simple but robust molecular methods to determine the haplotype structure of patients.[68]

GENETIC POLYMORPHISMS WITH INDIRECT EFFECTS ON DRUG RESPONSE

Polymorphisms in genes encoding proteins that are neither direct targets of medications nor involved in their disposition have been shown to alter the response to treatment in certain situations (Table 2). For example, inherited differences in coagulation factors can predispose women taking oral contraceptives to deep-vein or cerebral-vein thrombosis,[80] whereas polymorphisms in the gene for the cholesterol ester transfer protein have been linked to the progression of atherosclerosis with pravastatin therapy.[75]

Genetic variation in cellular ion transporters can also have an indirect role in predisposing patients to toxic effects of drugs. For example, patients with variant alleles for sodium or potassium transporters may have substantial morbidity or mortality resulting from drug-induced long-QT syndrome. A mutation in *KCNE2*, the gene for an integral membrane subunit that assembles with HERG to form I_{Kr} potassium channels, was identified in a patient who had cardiac arrhythmia after receiving clarithromycin.[76] Additional *KCNE2* variants have been associated with the development of a very long QT interval after therapy with trimethoprim–sulfamethoxazole, with sulfamethoxazole inhibiting potassium channels encoded by the *KCNE2* (8T→A) variant.[77] Because *KCNE2* variants occur in about 1.6 percent of the population and their effect on drug actions can cause death, they are excellent candidates for polygenic strategies to prevent serious drug-induced toxic effects.

Genetic polymorphism in the apolipoprotein E (*APOE*) gene appears to have a role in predicting responses to therapy for Alzheimer's disease and to lipid-lowering drugs.[70,71,82,83] There are numerous allelic variants of the human *APOE* gene (e.g., *APOE* $\epsilon 3$, *APOE* $\epsilon 4$, *APOE* $\epsilon 5$, etc.), which contain one or more single-nucleotide polymorphisms that alter the amino acid sequence of the encoded protein (e.g., apolipoprotein $\epsilon 4$ has a Cys112Arg change). In a study of treatment of Alzheimer's disease with tacrine, 83 percent of the patients without any *APOE* $\epsilon 4$ allele showed improvement in total response and cognitive response after 30 weeks, as compared with 40 percent of patients with at least one *APOE* $\epsilon 4$ allele.[72] However, the greatest individual improvement in this study was seen in a patient with a single *APOE* $\epsilon 4$ allele, the unfavorable genotype, illustrating that a single gene will not always predict the response to a given treatment.[72] Follow-up studies indicate that the interaction between tacrine treatment and *APOE* genotype was strongest for women, again suggesting that many genes are involved in determining the efficacy of a treatment.[84]

The molecular basis for an association between apolipoprotein genotype and tacrine efficacy has not been elucidated, but it has been postulated that the *APOE* $\epsilon 4$ genotype may have an effect on cholinergic dysfunction in Alzheimer's disease that cannot be consistently overcome by therapy with acetylcholinesterase inhibitors such as tacrine. A randomized, placebo-controlled study of the noradrenergic vasopressinergic agonist S12024 in patients with Alzheimer's disease found the greatest protection of cognition in patients with the *APOE* $\epsilon 4$ genotype.[85] Confirmation of these results may offer an approach to the selection of initial therapy for Alzheimer's disease, with S12024 or similar medications being recommended for patients carrying an *APOE* $\epsilon 4$ allele.

Both phenotypic analysis and genotypic analysis of the *APOE* polymorphism have shown an asso-

Figure 4 (facing page). Functional Consequence of Genetic Polymorphisms in the β_2-Adrenoreceptor (Coded by the *ADRB2* Gene) at Codons 16 and 27.

A homozygous Glu genotype at codon 27 is associated with greater venodilatation after the administration of isoproterenol (Panel A).[44] A homozygous Arg genotype at codon 16 is associated with greater airway response to oral albuterol (Panel B)[48] and greater desensitization to isoproterenol (Panel C).[44] FEV_1 denotes forced expiratory volume in one second.

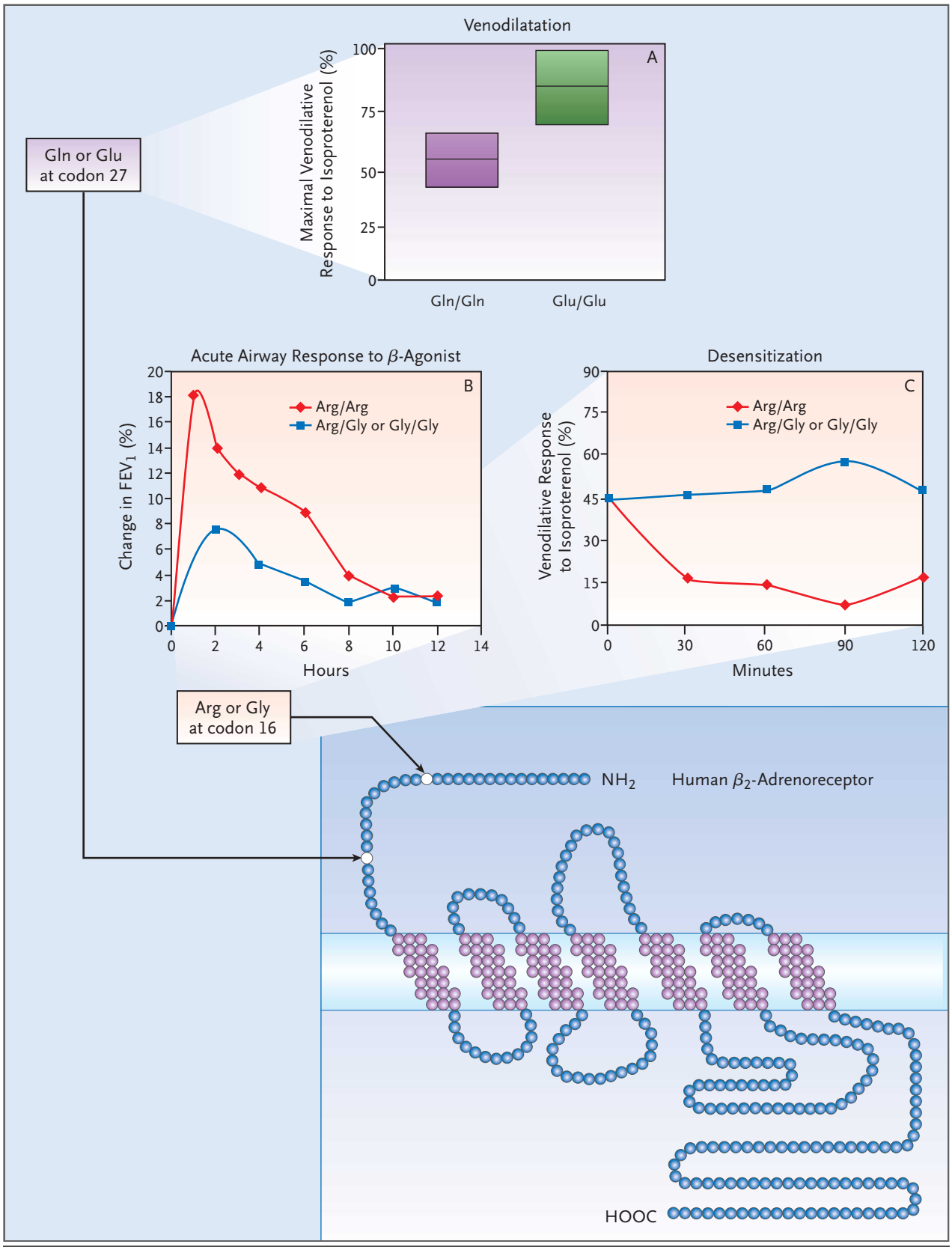


Table 2. Genetic Polymorphisms in Disease-Modifying or Treatment-Modifying Genes That Can Influence Drug Response.*

Gene or Gene Product	Disease or Response Association	Medication	Influence of Polymorphism on Drug Effect or Toxicity
Adducin	Hypertension	Diuretics	Myocardial infarction or strokes[69]
Apolipoprotein E (APOE)	Progression of atherosclerosis, ischemic cardiovascular events	Statins (e.g., simvastatin)	Enhanced survival[70,71]
Apolipoprotein E (APOE)	Alzheimer's disease	Tacrine	Clinical improvement[72]
HLA	Toxicity	Abacavir	Hypersensitivity reaction[73,74]
Cholesterol ester transfer protein (CETP)	Progression of atherosclerosis	Statins (e.g., pravastatin)	Slowing of progression of atherosclerosis by pravastatin[75]
Ion channels (HERG, KvLQT1, Mink, MiRP1)	Congenital long-QT syndrome	Erythromycin, terfenadine, cisapride, clarithromycin, quinidine	Increased risk of drug-induced torsade de pointes[76-78]
Methylguanine methyltransferase (MGMT)	Glioma	Carmustine	Response of glioma to carmustine[63]
Parkin	Parkinson's disease	Levodopa	Clinical improvement and levodopa-induced dyskinesias[79]
Prothrombin and factor V	Deep-vein thrombosis and cerebral-vein thrombosis	Oral contraceptives	Increased risk of deep-vein and cerebral-vein thrombosis with oral contraceptives[80]
Stromelysin-1	Atherosclerosis progression	Statins (e.g., pravastatin)	Reduction in cardiovascular events by pravastatin (death, myocardial infarction, stroke, angina, and others); reduction in risk of repeated angioplasty[81]

* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review.

ciation between *APOE* genotype and the response to lipid-lowering medications.[82,86-89] In most studies, patients with an *APOE* $\epsilon 2$ allele had the greatest diminution of low-density lipoprotein cholesterol after drug therapy. The decrease was greatest for those with *APOE* $\epsilon 2$, followed by *APOE* $\epsilon 3$ and then *APOE* $\epsilon 4$. This result was observed after treatment with a diverse range of lipid-lowering agents, including probucol, gemfibrozil, and many different 3-hydroxy-3-methylglutaryl-coenzyme A–reductase inhibitors (statins).[83] However, a significant effect of *APOE* genotype on the response to lipid-lowering agents has not been observed in all studies.[83]

In addition, although the *APOE4* allele was associated with less reduction in total and low-density lipoprotein cholesterol and a smaller increase in high-density lipoprotein cholesterol after fluvastatin therapy, there was no apparent influence of genotype on the progression of coronary artery disease or the incidence of clinical events.[88] Thus, prospective clinical evaluations with robust clinical end points and sufficient sample sizes are needed to define better the usefulness of the *APOE* genotype in selecting the treatment of hyperlipidemia and cardiovascular disease. The potential usefulness of the *APOE* genotype in predicting treatment response must be balanced by the concern that it could be used by insurance companies, health systems, and others to identify those at high risk for Alzheimer's disease, coronary artery disease, and possibly other illnesses.[82]

MOLECULAR DIAGNOSTIC METHODS FOR OPTIMIZING DRUG THERAPY

The potential is enormous for pharmacogenomics to yield a powerful set of molecular diagnostic methods that will become routine tools with which clinicians will select medications and drug doses for individual patients. A patient's genotype needs to be determined only once for any given gene, because except for rare somatic mutations, it does not change. Genotyping methods are improving so rapidly that it will soon be simple to test for thousands of single-nucleotide polymorphisms in one assay. It may be possible to collect a single blood sample from a patient, submit a small aliquot for analysis of a panel of genotypes (e.g., 20,000 single-nucleotide polymorphisms in 5000 genes), and test for those that are important determinants of drug disposition

and effects. In our opinion, genotyping results will be of greatest clinical value if they are reported and interpreted according to the patient's diagnosis and recommended treatment options.

CHALLENGES FOR THE FUTURE

There are a number of critical issues that must be considered as strategies are developed to elucidate the inherited determinants of drug effects. A formidable one is that the inherited component of the response to drugs is often polygenic (Fig. 1). Approaches for elucidating polygenic determinants of drug response include the use of anonymous single-nucleotide polymorphism maps to perform genome-wide searches for polymorphisms associated with drug effects, and candidate-gene strategies based on existing knowledge of a medication's mechanisms of action and pathways of metabolism and disposition. Both these strategies have potential value and limitations, as shown in previous reviews.[5,90,91] However, the candidate-gene strategy has the advantage of focusing resources on a manageable number of genes and polymorphisms that are likely to be important, and it has produced encouraging results in a number of studies.[20,52] The limitations of this approach are the incompleteness of knowledge of a medication's pharmacokinetics and mechanisms of action. Gene-expression profiling[92,93] and proteomic studies[94] are evolving strategies for identifying genes that may influence drug response.

One of the most important challenges in defining pharmacogenetic traits is the need for well-characterized patients who have been uniformly treated and systematically evaluated to make it possible to quantitate drug response objectively. To this end, the norm should be to obtain genomic DNA from all patients enrolled in clinical drug trials, along with appropriate consent to permit pharmacogenetic studies. Because of marked population heterogeneity, a specific genotype may be important in determining the effects of a medication for one population or disease but not for another; therefore, pharmacogenomic relations must be validated for each therapeutic indication and in different racial and ethnic groups. Remaining cognizant of these caveats will help ensure accurate elucidation of genetic determinants of drug response and facilitate the translation of pharmacogenomics into widespread clinical practice.

Supported in part by grants from the National Institutes of Health (R37 CA36401, R01 CA78224, U01 GM61393, U01 GM61394, and U01 GM63340), Cancer Center support grants (CA21765 and CA091842), a Center of Excellence grant from the State of Tennessee, a grant from the Siteman Cancer Center, and a grant from American Lebanese Syrian Associated Charities.

Dr. Evans became a member of the Clinical Genomics Advisory Board of Merck and a member of the Scientific Advisory Board for Signature Genetics and Gentris after this review was written, and he was formerly a member of the Scientific Advisory Board of PPGX. He currently serves as a consultant to Bristol-Myers Squibb. He holds no equity positions in any of these companies. Dr. Evans's laboratory is supported by National Institutes of Health grants. He receives no research support from public or private companies. Dr. McLeod's laboratory is supported by grants from the National Institutes of Health, as well as by research grants from Novartis Pharmaceuticals and Ortho Clinical Diagnostics for projects that do not overlap directly or indirectly with the contents of this article.

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