Genetic basis of drug metabolism

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The term “pharmacogenetics” was first coined by Friedrich Vogel in 1959, who defined it as the “study of the role of genetics in drug response.” It is one of the most rapidly growing areas and is becoming increasingly important in clinical pharmacy. The pharmacogenetics of drug-metabolizing enzymes is a prominent focus of this field, because genetic makeup is responsible for a significant portion of drug-induced toxicity; many drugs are metabolized by enzymes that are encoded by polymorphically expressed genes. Genotype analysis can be used to identify DNA changes in specific metabolic pathways that produce aberrant phenotypes. Hence, patients can be classified as extensive, intermediate, or poor metabolizers according to their ability to metabolize certain drugs. This classification can differentiate interpatient and intrapatient pharmacokinetic and pharmacodynamic variability; however, not all genetic polymorphisms of drug-metabolizing enzymes are clinically relevant. The potential for a clinically significant event is enhanced if the drug is widely used and has a narrow therapeutic range, if the enzyme pathway plays a major role in the elimination of the drug, or if the number of therapeutic alternatives is limited. With increasing pharmacogenetic evidence, interindividual differences in drug-related toxicity and therapeutic response are no longer idiosyncratic. Although much work is needed to develop applications of pharmacogenetic information for daily patient care, many success stories illustrate how pharmacogenetics can be used to guide therapy. Eventually, pharmacogenetic information may become a routine tool for providing ra-

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tional individualized therapeutics and patient care.

The pharmacogenetic differences in a number of phase-I enzymes, such as cytochrome P-450 (CYP) isoenzymes, dehydrogenases, and esterases, and phase-II (conjugating) enzymes have been extensively studied. This review introduces the concept of pharmacogenetics in the context of drug-metabolizing enzymes and highlights the polymorphisms in DNA sequences that lead to clinically significant alterations in drug-metabolizing enzyme activities. Many of these genetic variants (i.e., genotypes) were discovered after observing adverse reactions (i.e., phenotypes) after administering common doses of drugs to patients. We have focused on the most common single nucleotide polymorphisms (SNPs), the inherited nature of their deficiency, their frequency, and the clinical importance of drug-metabolizing enzyme variants. Most drug-metabolizing enzymes discussed in this review (e.g., CYP isoenzymes, N-acetyltransferase) are located primarily in the liver and, to a lesser extent, in other organs, such as the small intestine.

Common terminology

DNA consists of four bases: adenine, guanine, thymine, and cytosine. Any combination of three nucleic acids can form a codon, which is transcribed into mRNA and translated into a particular amino acid (e.g., ACG encodes for threonine). The stop codon, TAG, terminates protein synthesis. An incorrectly placed stop codon in a gene, caused by mutation, prematurely truncates an amino acid chain and may form a nonfunctional protein. Many of the variations in the human genome are single base changes, termed SNPs. A mutation of one nucleotide of a codon may result in either a change in the coded amino acid (nonsynonymous SNP) or no change (silent polymorphism or synonymous SNP). Since each person has a pair of each chromosome, he or she has two alleles for each gene, one on each chromosome. Different alleles produce variations in inherited characteristics, such as eye color and blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one). Two identical alleles result in a homozygous dominant or homozygous recessive trait of that gene. A combination of two different alleles leads to a heterozygous trait. One or more genes that code for a particular protein, such as an enzyme or a receptor, may be expressed in different amounts in different tissues. In this review, all individual alleles (or genes) are referenced by their gene name (e.g., CYP2D6), followed by an asterisk and an Arabic number (e.g., CYP2D6*1 designates the wild-type allele and CYP2D6*3 is a mutant allele).

Glucose-6-phosphate dehydrogenase

Phenotypes demonstrating variations in people’s response to certain drugs were first discovered in the early 1950s when antimalarial drugs were found to cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD, expressed in all of the body’s tissues, controls the flow of carbon through the pentose phosphate pathway, produces NADPH for reductive biosynthesis, and maintains oxidation-reduction in the cell to keep glutathione in a reduced state. The absence of reduced glutathione due to G6PD deficiency allows oxidative drugs to oxidize sulfahydroxyl groups of hemoglobin, leading to hemolysis. Currently, over two dozen drugs, including primaquine, sulfones, sulfonylamides, nitrofurans, vitamin K analogues, cefotetan, and chloramphenicol, are known to cause hemolytic anemia in G6PD-deficient patients. G6PD deficiency is a sex-linked (chromosome X) recessive trait and a widespread polymorphism, with more than 400 known variants and affecting more than 400 million people worldwide. However, the vast majority of affected individuals are asymptomatic. Only 30 different functional mutations in the gene have been reported, virtually all of which are found in the region of the gene that codes for the protein.

The consequence of these genetic polymorphisms is low G6PD activity, resulting in reduced glutathione concentrations in erythrocytes and subsequent clinical manifestation of hemolytic anemia following the ingestion of certain drugs. The prevalence of G6PD deficiency differs among ethnic groups. For instance, males of African and Mediterranean descent more frequently express the trait. Two types of mutations are commonly found in Africans, G6PD A and G6PD A(-). The former protein produces normal red cell activity, while the latter produces only about 10% of the normal activity and is unstable in vivo. In patients with G6PD A, an adenosine-to-guanine substitution at nucleotide 376 (A376G) mutation causes an aspartic acid residue to replace an asparagine residue. There are three different G6PD A(-) variants in one allele. The A376G mutation occurs in all people, but the enzyme deficiency is caused by a second amino acid substitution, usually a G202A mutation, resulting in a valine-to-methionine substitution at codon 68 (Val68Met). Other mutations are Val690Met and Val968Met. In Mediterranean peoples, the most common mutation is a C563T substitution resulting in an amino acid change (Ser188Phe).

Cases of drug-induced hemolytic anemia have also been described in patients treated with cyclosporine, tacrolimus, penicillin, and cefotetan. The risk and severity of hemolysis are thought to be associated with dose, duration of therapy, and other oxidant stresses, such as infection.
and environmental factors. Because of these confounding factors, genotyping patients for G6PD deficiency is not warranted, since the toxicity is rare and not typically life-threatening and the genotype does not adequately predict the development of hemolytic anemia. For example, some patients with these mutations experience toxicity after drug administration, and others do not. In addition, the treatment for drug-induced oxidative hemolytic anemia is merely cessation of drug administration, with blood transfusion and corticosteroid administration warranted in severe cases.

G6PD deficiency is an example of how genotypic analysis was developed about half a century after the clinical observation was made, and further characterization of the genetic mutation provided no added clinical advantages. Although genetic constitution may be at the core of explaining drug toxicity and efficacy, genotyping may not always directly affect therapy or predict patient outcomes.

N-Acetyltransferase

The acetylation polymorphism illustrates another genetic polymorphism of a drug-metabolizing enzyme studied in the early era of pharmacogenetics. N-acetyltransferase (gene, NAT), a phase-II conjugating liver enzyme, catalyzes the N-acetylation (usually deactivation) and O-acetylation (usually activation) of arylamine carcinogens and heterocyclic amines. The slow acetylator phenotype often experiences toxicity from drugs such as isoniazid, sulfonamides, procainamide, and hydralazine, whereas the fast acetylator phenotype may not respond to isoniazid and hydralazine in the management of tuberculosis and hypertension, respectively. During the development of isoniazid, isoniazid plasma concentrations were observed in a distinct bimodal population after a standard dose. Patients with the highest plasma isoniazid levels were generally slow acetylators and they suffered from peripheral nerve damage, while fast acetylators were not affected. Slow acetylators are also at risk for sulfonamide-induced toxicity and can suffer from idiopathic lupus erythematosus while taking procainamide. The slow acetylator phenotype is an autosomal recessive trait. Studies have shown large variations of the slow acetylator phenotype among ethnic groups: 40–70% of Caucasians and African-Americans, 10–20% of Japanese and Canadian Eskimos, more than 80% of Egyptians, and certain Jewish populations are slow acetylators. In East Asia, the further north the geographic origin of the population, the lower the frequency of the slow acetylator gene. The reason for this trend is unknown, but it has been speculated that differences in dietary habits or the chemical or physical environment may be contributing factors.

Allelic variation at the NAT2 gene locus accounts for the polymorphism seen with acetylation of substrate drugs. There are 27 NAT2 alleles that have been reported. NAT2 is an unusual gene because it consists of open-reading frames (i.e., protein-coding regions) without introns. Most variant NAT2 alleles involve two or three point mutations. For example, the variant NAT2*5B differs from the wild-type at three nucleotide positions, 341, 481, and 803; NAT2*6A has two changes at positions 282 and 590; NAT*13 has one point mutation at 282; and NAT2*7A has two changes at positions 282 and 857. NAT2*5B and *6A account for 72–75% of all the variant NAT2 alleles, which includes at least 94% of all variant alleles in Caucasians, Japanese, and Hispanics and 83% of the NAT2 alleles in African-Americans. NAT2*5B is the most common allele in Caucasians (40–46%), but occurs at a very low frequency in Japanese (0.5%). NAT*6A, *7B, and *13 share a mutation at C282T. NAT*5A, *5B, *6A, *7A, *7B, and *13 are associated with the slow acetylator phenotype as a result of a decrease in the amount of NAT2 protein. The protein expressed from NAT2*5A, *5B, and *5C genes has lower activities than *6A and *7B, whereas *13 has normal activity.

Currently, the importance of these variants in NAT2 is most studied for their association with a modestly increased risk for cancers, possibly because of prolonged exposure of the body to chemicals, drugs, or metabolites compared with fast acetylators. A recent preliminary result suggested that impaired isoniazid metabolism is associated with point mutations in NAT2 in a small Japanese population. This exciting result awaits large population studies to establish clearly the relationship between the NAT2 genotype and isoniazid acetylation. It still takes some time to establish the clinical utility of NAT2 genotype analysis to independently predict isoniazid acetylation. However, genotype NAT2 mutations could be an addition to the traditional therapeutic drug monitoring for isoniazid in the near future.

Genetic polymorphisms in the CYP isoenzymes

The CYP isoenzyme superfamily comprises over 50 heme-containing proteins that catalyze the oxidative metabolism of many structurally diverse drugs and chemicals. It is one of the most widely studied drug-metabolizing-isozyme systems. Its name is derived from the characteristic maximum spectral absorbance at 450 nm, when it is in its reduced state. CYP exists as multiple forms or isozymes, with each having variable distribution in different tissues. The basis for nomenclature is dependent on the similarity among the genetic sequences that encode the isozymes. When the DNA sequence of the gene for one CYP isozyme is less than 40% similar to that of another, the two isozymes belong to different CYP families. Each enzyme family is represented by
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an Arabian number (e.g., CYP1) and further divided into subfamilies in which the isoenzymes’ corresponding DNA sequences are approximately 70% identical. For example, CYP1A2 belongs to family 1 and subfamily A; the last Arabic number indicates a particular gene encoding for the isoenzyme within the A subfamily. More detailed descriptions of the CYP nomenclature are found in the literature.31,32

CYP2D6. CYP2D6 isoenzyme metabolizes 25-30% of all clinically used medications, including dextromethorphan, β-blockers (e.g., metoprolol), antiarrhythmics, antidepressants (e.g., fluoxetine, fluvoxamine, flunitrazepam, naproxen), antipsychotics (e.g., haloperidol, risperidone), morphine derivatives, and many other drugs. Variability in the interindividual responses to these agents is often caused by genetic polymorphisms in CYP2D6, also termed the debrisoquin/sparteine genetic polymorphism in reference to the drugs that are its substrates that led to its discovery.33 Unlike the CYP3A family, CYP2D6 is a noninducible enzyme; thus, its genotype offers a high predictability of CYP2D6-mediated metabolism.

CYP2D6, the gene encoding CYP2D6 isoenzyme, has the most variations of all genes for CYP isoenzymes, with more than 75 allelic variants identified to date, resulting from point mutations, single base-pair deletions or additions, gene rearrangements, and deletion of the entire gene. These mutations result in either a reduction or complete loss of activity.34 Administering a CYP2D6 substrate as a probe drug (e.g., bufuralol, dextromethorphan, debrisoquin, sparteine) and measuring the metabolite-to-parent drug ratio in the urine (metabolic ratio) differentiate extensive metabolizers from poor metabolizers. Genotype-phenotype studies have revealed that poor metabolizers possess two nonfunctional alleles and that the phenotype is an autosomal recessive trait.35,36 An ultrarapid metabolizer phenotype has also been identified and found to result from gene duplication (up to 13 copies of CYP2D6).37 Poor metabolizers are more likely to have adverse effects from drugs that are substrates of the isoenzyme and decreased efficacy from drugs requiring CYP2D6-mediated activation (e.g., codeine is converted into morphine by CYP2D6), while extensive and ultrarapid metabolizers may have therapeutic failure with drugs activated by CYP2D6 (e.g., standard antidepressant doses).38 Because CYP2D6 isoenzyme metabolizes such a large number of drugs used in the clinical setting, pharmacists have an important role in drug monitoring, including identifying CYP2D6 substrates, monitoring for drug efficacy and toxicity, and understanding the phenotypic and genotypic tools available.

The frequency of the phenotype of poor metabolizers differs among ethnic groups. Less than 1% of Asians, 2-5% of African-Americans, and 6-10% of Caucasians are poor metabolizers of CYP2D6.3 The most common variant alleles in Caucasians are CYP2D6*3, *4, *5, and *6, which account for about 98% of poor metabolizers.39 The CYP2D6*3A allele is a frameshift mutation caused by a single adenine deletion in exon 5 that results in a premature stop codon. CYP2D6*4A contains a G-to-A transition in the last nucleotide of intron 3, producing a splicing defect and subsequent frameshift in the open-reading frame and premature stop codon.40 The CYP2D6*5 variant is caused by a deletion of the entire CYP2D6 gene.41 Although poor metabolizers may be homozygous for one particular defective allele (e.g., CYP2D6*4A/*4A), compound heterozygosity (e.g., CYP2D6*4A/*6) is common. Despite a lower frequency of poor metabolizers, Asian and African-American populations tend to have reduced CYP2D6 activity compared with Caucasians because of a lower occurrence of nonfunctional alleles (e.g., *3, *4, *5, *6), but a higher frequency of alleles associated with reduced activity (e.g., *10, *17).42

Genotyping CYP2D6 has been shown to successfully predict the clearance of fluoxetine, fluvoxamine, desipramine, and mexiletine.43-46 In some instances, the genotype for CYP2D6 has been useful in predicting adverse effects associated with antidepressants and neuroleptics. Arrhythmias, nausea, and vomiting occurred selectively in poor metabolizers during treatment with mexiletine, propafenone, and debrisoquin, likely because of elevated plasma drug concentrations.46-48

Currently, preliminary dosage recommendations based on CYP2D6 genotypes are available for antidepressants.49 This gives us a glimpse of how pharmacogenetics can suggest dose regimens for a small population of patients. Prospective studies are warranted to address whether genotype-based dose recommendations have a positive outcome on therapy.

CYP2C9. Impaired metabolism of drugs metabolized by the CYP2C9 isoenzyme, such as phenytoin, S-warfarin, tolbutamide, losartan, and nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., ibuprofen, diclofenac, piroxicam, tenoxicam, mefenamic acid) has been noted.51,52

The CYP2C9 genotype was first observed to be correlated with the pharmacokinetics of tolbutamide. Three allelic variants of the CYP2C9 gene have been identified that are associated with decreased enzyme activity.52,53 The variant alleles CYP2C9*2 (Arg144Cys) and *3 (Ile359Leu) contain single nucleotide polymorphisms that result in single amino acid substitutions. CYP2C9*2 and *3 were associated with a 5.5- and 27.0-fold decrease in the intrinsic clearance of S-warfarin, respectively, compared with the wild-type allele.54,55 As such, clinical consequences of the CYP2C9*3 allele are likely to be more dramatic than those of CYP2C9*2. Homozygous
CYP2C9*3 alleles were found in poor metabolizers of phenytoin, glipizide, tolbutamide, and losartan. Increased risks of bleeding were observed in patients with mutant alleles (poor metabolizers), and subsequent dosage adjustments were required.\textsuperscript{50,56,57} Phenytoin is a substrate of both CYP2C9 and CYP2C19 isoenzymes, but CYP2C9 is responsible for its metabolism to a greater extent; thus, mutant alleles encoding the CYP2CP gene have a greater effect on the clinical toxicity of phenytoin. The CYP2C9*3 mutant allele occurs in approximately 6–9% of Caucasians and Asians.\textsuperscript{52} CYP2C9*2 occurs in approximately 8–20% of Caucasians and less frequently in African-Americans and is virtually absent in Asians. Individuals who require a low dose of warfarin to maintain optimum anticoagulation have a slightly higher frequency of variant CYP2C9 alleles than those who require a higher dose.\textsuperscript{58} One study found that life-threatening bleeding was four times more likely in a group of patients requiring a lower dose of warfarin. These patients also had more difficulty establishing therapeutic anticoagulation, which led to multiple visits to the hospital and prolonged hospital stays resulting from serious or life-threatening bleeding events, and additional required laboratory testing.\textsuperscript{56} CYP2C9 genotyping may help identify high-risk patients who are candidates for lower warfarin doses, more frequent monitoring, or alternative drug treatments.

In addition to the metabolism of warfarin and phenytoin, polymorphisms in CYP2C9 have the potential to affect the toxicity of several NSAIDs. For example, homozygous CYP2C9*3 alleles may result in slower metabolism of these drugs. However, there have been no reports correlating CYP2C9 genotype to the pharmacokinetics of NSAIDs. Since NSAIDs have relatively high therapeuetic indices, these polymorphisms may have less of an impact on clinical consequences. It is worth mentioning that a recent study has elucidated the role of CYP2C9 genotype on the metabolism of celecoxib, a cyclooxygenase-2 inhibitor.\textsuperscript{59} The study found that patients either heterozygous or homozygous who have at least one copy of the CYP2C9*2 (i.e., CYP2C9*1/*2 or CYP2C9*2/*2) or CYP2C9*3 (i.e., CYP2C9*1/*3 or CYP2C9*3/*3) allele would have an increased celecoxib plasma area-under-the-concentration-time curve as a result of the reduced drug metabolism. The clinical significance of this observation remains unclear.

CYP2C9 genotyping may affect the clinical use of warfarin because of the relatively high prevalence of poor metabolizers, severe outcomes as a consequence of drug overdose, and frequency with which it is prescribed. CYP2C9 genotyping assays are available only for clinical research, but commercial assays are being developed.\textsuperscript{60} Genotype testing for CYP2C9 will allow pharmacists to develop dose recommendations to reduce the risk of adverse drug reactions in patients receiving warfarin and screen for high-risk patients who are candidates for lower initial warfarin doses.\textsuperscript{56}

**CYP2C19.** CYP2C19 isoenzyme metabolizes several pharmacologically important therapeutic agents. Extensive and poor metabolizers exist for 5-mephenytoin, omeprazole and other proton-pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline. The phenotype was initially determined using mephenytoin as a probe drug because of the significant correlation between formation of the 4-hydroxymephenytoin metabolite and the amount of CYP2C19 in human liver microsomes.\textsuperscript{61} Phenotyping of CYP2C19 with mephenytoin is limited because of concerns about the use of the probe drug, low urinary metabolite concentration, and stability of the metabolite in urine. More recently, omeprazole and other substrates have been used in phenotyping studies. The poor metabolizer phenotype is a result of two non-functional alleles and is inherited as an autosomal recessive trait. In contrast, the extensive metabolizer phenotype consists of both heterozygous and homozygous dominant genotypes, but they usually cannot be distinguished by phenotyping methods.

At least five mutant alleles have been identified.\textsuperscript{62} The most common variant alleles in poor metabolizers, CYP2C19*2 and *3, arise from single base-pair substitutions in exons 4 (CYP2C19*3) and 5 (CYP2C19*2) that introduce premature stop codons and truncated polypeptide chains with no functional activity.\textsuperscript{63} CYP2C19*2 is identified with a 40 base-pair deletion at the beginning of the exon, which shifts the reading frame to create an aberrant splice site and produces a premature stop codon about 20 amino acids downstream.\textsuperscript{64} CYP2C19*3 is mainly found in the Japanese population. There are also ethnic differences in the frequency of the poor metabolizer phenotype. About 3–5% of Caucasians and 12–23% of most Asian populations are poor metabolizers.\textsuperscript{65,66}

Although relatively few drugs are metabolized by CYP2C19, pronounced pharmacodynamic effects tend to be seen in Asians treated with omeprazole because of the higher frequency of poor metabolizers.\textsuperscript{67} Poor metabolizers of mephenytoin also have higher serum omeprazole metabolite ratios than extensive metabolizers because of impaired omeprazole metabolism.\textsuperscript{68} Results of a study by Furuta et al.\textsuperscript{69} suggested that the CYP2C19 genotype might influence the cure rates for Helicobacter pylori infection in patients with peptic ulcers. The cure rate was 100% in poor metabolizers, 60% in patients with heterozygous genotypes, and 29% in patients with homozygous wild-types. This may be explained by the higher accumulation of plasma omeprazole concentrations in poor
metabolizers, resulting in a greater degree of gastric acid suppression. Similar to omeprazole, the extent of lansoprazole and pantoprazole metabolism is highly dependent on CYP2C19 genotype. Thus, interindividual differences in plasma concentrations of these proton-pump inhibitors may be prospectively predicted by genetically determined CYP2C19 status. However, the contributions of CYP2C19 isoenzyme to the metabolism of these proton-pump inhibitors are not evenly distributed; omeprazole is more extensively metabolized by CYP2C19 than pantoprazole, lansoprazole, and rabeprazole.

Diazepam is another example of a CYP2C19 substrate affected by this polymorphism. The half-life of diazepam in plasma is significantly prolonged in individuals who are homozygous for the mutant CYP2C19*2 allele (80 hours) compared with heterozygotes (64 hours) and people with homozygous wild-type CYP2C19 (20 hours). Asian populations have been reported to exhibit slower diazepam metabolism than Caucasians, possibly due to a higher frequency of CYP2C19*2 and CYP2C19*3 genotypes. Poor metabolizers of CYP2C19 may be at a higher risk for diazepam toxicity, and caution must be exercised in dosing diazepam.

**CYP3A subfamily.** CYP3A enzymes are the predominant subfamily of CYP enzymes, making it one of the most important drug-metabolizing enzymes. The genes for CYP3A enzymes are expressed primarily in the liver and small intestines. Hepatic CYP3A4 isoenzyme has been estimated to metabolize almost 50% of currently used drugs as well as endogenous and exogenous corticosteroids. Intestinal CYP3A4 isoenzyme contributes significantly to the first-pass metabolism of orally administered drugs. There is large interindividual variability in genetic expression for CYP3A, exceeding 30-fold in some populations, but evidence for polymorphic activity has been elusive until recently. Consequently, these variations play a significant role in the variability of oral bioavailability and metabolism of CYP3A substrates, including HIV protease inhibitors, benzodiazepines, calcium channel blockers, hydroxymethylglutaryl coenzyme A-reductase inhibitors, antineoplastic drugs, nonsedating antihistamines, and immunosuppressants. These variations can result in differences in drug efficacy and toxicity among individuals.

CYP3A activities are the sum of the activities of at least three CYP3A isoenzymes: CYP3A4, CYP3A5, and CYP3A7. Interindividual variability due to CYP3A4 activity alone may vary by up to 50-fold. Functional consequences of a polymorphism in the CYP3A4 promoter region (A290G) (i.e., CYP3A4*1B) have been studied as a possible cause of this variability, but the effects of this SNP have not been clearly defined. Ethnic variation has been suggested as a possible reason, which may explain the higher frequency of the homozygous mutation in Ghanaians in African (51%) than in Scottish Caucasian (0%) and Saudi populations (1%).

It is estimated that CYP3A5 isoenzyme is only present in 10–30% of liver samples tested. Recently, CYP3A5 isoenzyme was found to account for at least 50% of the total CYP3A content in people who carry the wild-type CYP3A5*1 allele (96–98% of the combined population), suggesting that CYP3A5 may play a significant role in the metabolism of CYP3A substrates. Only people with at least one wild-type CYP3A5*1 allele express large amounts of CYP3A5 isoenzyme, resulting in a 2.5-fold increase in clearance of the probe drug (midazolam). The most common cause of loss of the expression of the CYP3A5 gene is the deletion of exon 7, causing the deletion of exon 7 and reducing CYP3A activity. CYP3A5*1 is more frequently expressed in non-Caucasian populations (30% of Caucasians, Japanese, and Mexicans; 40% of Chinese; and 60% of African-Americans). However, these populations may metabolize CYP3A substrates more rapidly.

CYP3A5 appears to be an important genetic contributor to interindividual and interracial differences in CYP3A-dependent drug metabolism. Patients expressing both wild-type CYP3A4 and CYP3A5 genotypes extensively metabolize CYP3A substrates, which may lead to a lack of therapeutic effect. Prediction of drug interactions involving the inhibition and metabolism of CYP3A will continue to be a challenge and clinically important because of the diverse role CYP3A plays in the metabolism of currently available and future drugs. However, the variability observed in CYP3A activity may not be solely due to polymorphisms in the genes for these isoenzymes. The recent discovery of the PXR gene, a regulator of CYP gene expression, provides another possible factor for the variability in drug metabolism and a molecular basis for drug interactions. Identifying the regulatory mechanisms of enzyme induction and polymorphisms within these regulatory elements and high-throughput screening for future drugs may allow accurate prediction of CYP3A enzyme induction and drug interactions. Specific guidelines for the use of CYP3A pharmaco- genetics to modulate drug therapy are under development.

**Summary.** Major genetic polymorphisms that affect drug-metabolizing enzymes are summarized in Table 1. The technology to identify SNPs is available, and databases that house these SNPs and gene sequence infor-
mation are rapidly growing and readily accessible. In the past, pharmacogenetics has been used to explain clinically overt toxicity or the lack of efficacy in a subset of patients. As the field continues to develop, pharmacogenetics will play an important role in prospectively predicting a patient’s drug activation and detoxification status, such that a therapeutic intervention can be made prior to drug administration without exposing the patient to drug toxicity or therapeutic failure. Further, recent evidence indicates that genotyping tests can more accurately predict a person’s ability to metabolize certain drugs than an approach based solely on ethnic or geographic groups.10,11 Although a genetic basis is preferable to less objective measures, such as skin color, currently there is no algorithm that can provide a comprehensive predictive surrogate for all drug-metabolizing-enzyme SNPs. Pharmacogenetics has thus far provided a drug–gene relationship to drug response and has contributed in learning how to administer certain drugs more effectively and safely. Functional consequences of polymorphisms within drug metabolizing enzymes become better understood and genotype analysis becomes less costly, pharmacogenetics may lead to the individualization of medication dosing and improved therapeutics.60

Conclusion
Pharmacogenetics has elucidated the genetic basis for interindividual variability in drug response. Pharmacogenetics will continue to play a key role in defining strategies to optimize drug therapy.

References

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<tr>
<th>Enzyme*</th>
<th>Variant Allele(s)</th>
<th>Frequency of PMs b</th>
<th>Drugs with Affected Metabolism</th>
<th>Consequence(s)</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>G6PD A, G6PD A(–)</td>
<td>G6PD</td>
<td>40–70% of Caucasians and African-Americans</td>
<td>Increased relative risk of cancers and drug toxicity</td>
<td>Cessation of sulfa drugs</td>
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<tr>
<td>NAT*5B</td>
<td>40–70% of Caucasians and African-Americans</td>
<td>Isoniazid, sulfonamides, procarbazine, hydralazine</td>
<td>Increased relative risk of cancers and drug toxicity</td>
<td>Cessation of sulfa drugs</td>
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<tr>
<td>CYP2D6<em>2A, CYP2D6</em>3, *4, *5, *6, *10, *17</td>
<td>6–10% of Caucasians, 2–5% of African-Americans, 1% of Asians</td>
<td>β-receptor antagonists, antiarrhythmics, antidepressants, antipsychotics, morphine derivatives</td>
<td>Lack of analgesic effects from codeine, standard antidepressant dosage ineffective</td>
<td>Dosage adjustment in PMs</td>
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<tr>
<td>CYP2C9</td>
<td>CYP2C9<em>2, CYP2C9</em>3</td>
<td>6–8% of Caucasians</td>
<td>Warfarin, phenytoin, glipizide, tolbutamide, losartan, NSAIDs'</td>
<td>Increased bleeding episodes from standard warfarin dose, low blood sugar levels in PMs</td>
<td>Dosage adjustment needed for PMs to achieve optimal therapeutic benefit</td>
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<tr>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>3–5% of Caucasians, 12–23% of Asians</td>
<td>S-mephénytoin, omeprazole, diazepam, propranolol, imipramine, amitriptyline</td>
<td>Increased omeprazole AUC and higher H. pylori eradication rate in PMs, prolonged half-life of diazepam and increased risk of diazepam toxicity in Asians</td>
<td>Dosage adjustment needed for PMs to achieve optimal therapeutic benefit</td>
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aG6PD = glucose-6-phosphate dehydrogenase, NAT = N-acetyltransferase, CYP = cytochrome P-450 isoenzyme system.
bPMs = poor metabolizers.
cNSAIDs = nonsteroidal antiinflammatory drugs.
dAUC = area-under-the-concentration–time curve.
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