REVIEW ARTICLE

GENOMIC MEDICINE

Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D., *Editors*

Inheritance and Drug Response

Richard Weinshilboum, M.D.

From the Departments of Molecular Pharmacology and Experimental Therapeutics and Medicine, Mayo Medical School, Mayo Clinic, and Mayo Foundation, Rochester, Minn. Address reprint requests to Dr. Weinshilboum at the Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Medical School–Mayo Clinic–Mayo Foundation, Rochester, MN 55905, or at weinshilboum.richard@mayo.edu.

THE PROMISE OF PHARMACOGENETICS, THE STUDY OF THE ROLE OF INheritance in the individual variation in drug response, lies in its potential to identify the right drug and dose for each patient. Even though individual differences in drug response can result from the effects of age, sex, disease, or drug interactions, genetic factors also influence both the efficacy of a drug and the likelihood of an adverse reaction.[1-3] This article briefly reviews concepts that underlie the emerging fields of pharmacogenetics and pharmacogenomics, with an emphasis on the pharmacogenetics of drug metabolism. Although only a few examples will be provided to illustrate concepts and to demonstrate the potential contribution of pharmacogenetics to medical practice, it is now clear that virtually every pathway of drug metabolism will eventually be found to have genetic variation. The accompanying article by Evans and McLeod[4] expands on many of the themes introduced here.

Once a drug is administered, it is absorbed and distributed to its site of action, where it interacts with targets (such as receptors and enzymes), undergoes metabolism, and is then excreted.[5,6] Each of these processes could potentially involve clinically significant genetic variation. However, pharmacogenetics originated as a result of the observation that there are clinically important inherited variations in drug metabolism. Therefore, this article — and the examples highlighted — focuses on the pharmacogenetics of drug metabolism. However, similar principles apply to clinically significant inherited variation in the transport and distribution of drugs and their interaction with their therapeutic targets. The underlying message is that inherited variations in drug effect are common and that some tests that incorporate pharmacogenetics into clinical practice are now available, with many more to follow.

The concept of pharmacogenetics originated from the clinical observation that there were patients with very high or very low plasma or urinary drug concentrations, followed by the realization that the biochemical traits leading to this variation were inherited. Only later were the drug-metabolizing enzymes identified, and this discovery was followed by the identification of the genes that encoded the proteins and the DNA-sequence variation within the genes that was associated with the inherited trait. Most of the pharmacogenetic traits that were first identified were monogenic — that is, they involved only a single gene — and most were due to genetic polymorphisms; in other words, the allele or alleles responsible for the variation were relatively common. Although drug effect is a complex phenotype that depends on many factors, early and often dramatic examples involving succinylcholine and isoniazid facilitated acceptance of the fact that inheritance can have an important influence on the effect of a drug. Today there is a systematic search to identify functionally significant variations in DNA sequences in genes that influence the effects of various drugs.[4]

PHARMACOGENETICS OF DRUG METABOLISM

Metabolism usually converts drugs to metabolites that are more water soluble and thus more easily excreted.[5] It can also convert prodrugs into therapeutically active compounds, and it may even result in the formation of toxic metabolites. Pharmacologists classify pathways of drug metabolism as either phase I reactions (i.e., oxidation, reduction, and hydrolysis) or phase II, conjugation reactions (e.g., acetylation, glucuronidation, sulfation, and methylation).[5] The names used to refer to these pathways for drug metabolism are purely historical, so phase II reactions can precede phase I reactions and often occur without prior oxidation, reduction, or hydrolysis. However, both types of reaction most often convert relatively lipid-soluble drugs into relatively more water-soluble metabolites (Fig. 1).

The finding, approximately 40 years ago, that an impairment in a phase I reaction — hydrolysis of the muscle relaxant succinylcholine by butyrylcholinesterase (pseudocholinesterase) — was inherited served as an early stimulus for the development of pharmacogenetics.[7] Approximately 1 in 3500 white subjects is homozygous for a gene encoding an atypical form of butyrylcholinesterase[8] and is relatively unable to hydrolyze succinylcholine, thus prolonging the drug-induced muscle paralysis and consequent apnea.[9] At almost the same time, it was observed that a common genetic variation in a phase II pathway of drug metabolism — N-acetylation — could result in striking differences in the half-life and plasma concentrations of drugs metabolized by N-acetyltransferase. Such drugs included the antituberculosis agent isoniazid,[10] the antihypertensive agent hydralazine,[11] and the antiarrhythmic drug procainamide,[12] and this variation had clinical consequences in all cases.[13] The bimodal distribution of plasma isoniazid concentrations in subjects with genetically determined fast or slow rates of acetylation in one of those early studies[10] strikingly illustrates the consequences of inherited variations in this pathway for drug metabolism (Fig. 2). These early examples of the potential influence of inheritance on the effect of a drug set the stage for subsequent studies of genetic variation in other pathways of drug biotransformation.

PHARMACOGENETICS OF PHASE I DRUG METABOLISM

The cytochrome P-450 enzymes, a superfamily of microsomal drug-metabolizing enzymes, are the most important of the enzymes that catalyze phase I drug metabolism.[5] One member of this family, cytochrome P-450 2D6 (CYP2D6), represents one of the most intensively studied and best understood examples of pharmacogenetic variation in drug metabolism. The CYP2D6 genetic polymorphism was originally discovered as a result of striking differences in the pharmacokinetics and therapeutic effects of drugs metabolized by this enzyme — drugs as diverse as codeine, dextromethorphan, metoprolol, and nortriptyline, to mention only a few of the scores of agents metabolized by this enzyme.[14]

Approximately 5 to 10 percent of white subjects were found to have a relative deficiency in their ability to oxidize the antihypertensive drug debrisoquin.[15] They also had an impaired ability to metabolize the antiarrhythmic and oxytocic drug sparteine.[16] Subjects with poor metabolism of these two drugs had lower urinary concentrations of metabolites and higher plasma concentrations of the parent drug than did subjects with extensive metabolism. Furthermore, the drugs had an exaggerated effect in these subjects, and family studies demonstrated that poor oxidation of debrisoquin and sparteine was inherited as an autosomal recessive trait.[15,16] That is, subjects with poor metabolism had inherited two copies of a gene or genes that encoded either an enzyme with decreased CYP2D6 activity or one with no activity.

A plot of the ratio of urinary debrisoquin to 4-hydroxydebrisoquin — a so-called metabolic ratio — is shown in Figure 3.[17] The higher the metabolic ratio, the less metabolite was excreted. Therefore, subjects with poor metabolism are shown, counterintuitively, at the far right of the graph, with a few subjects at the far left of the frequency distribution who are now classified as having ultrarapid metabolism.[18] As described subsequently, such subjects may have multiple copies of the gene for CYP2D6.[18] Therefore, debrisoquin and sparteine represented "probe drugs" — compounds that could be used to classify subjects as having either poor metabolism or extensive metabolism. That strategy, the administration of a probe compound metabolized by a genetically polymorphic enzyme, became a standard technique used in many pharmacogenetic studies. Unfortunately, even though it was useful for research purposes, the approach was not easily adapted for the routine clinical laboratory. Therefore, the application of molecular genetic techniques to pharmacogenetics not only has made it possible to determine underlying molecular mech-
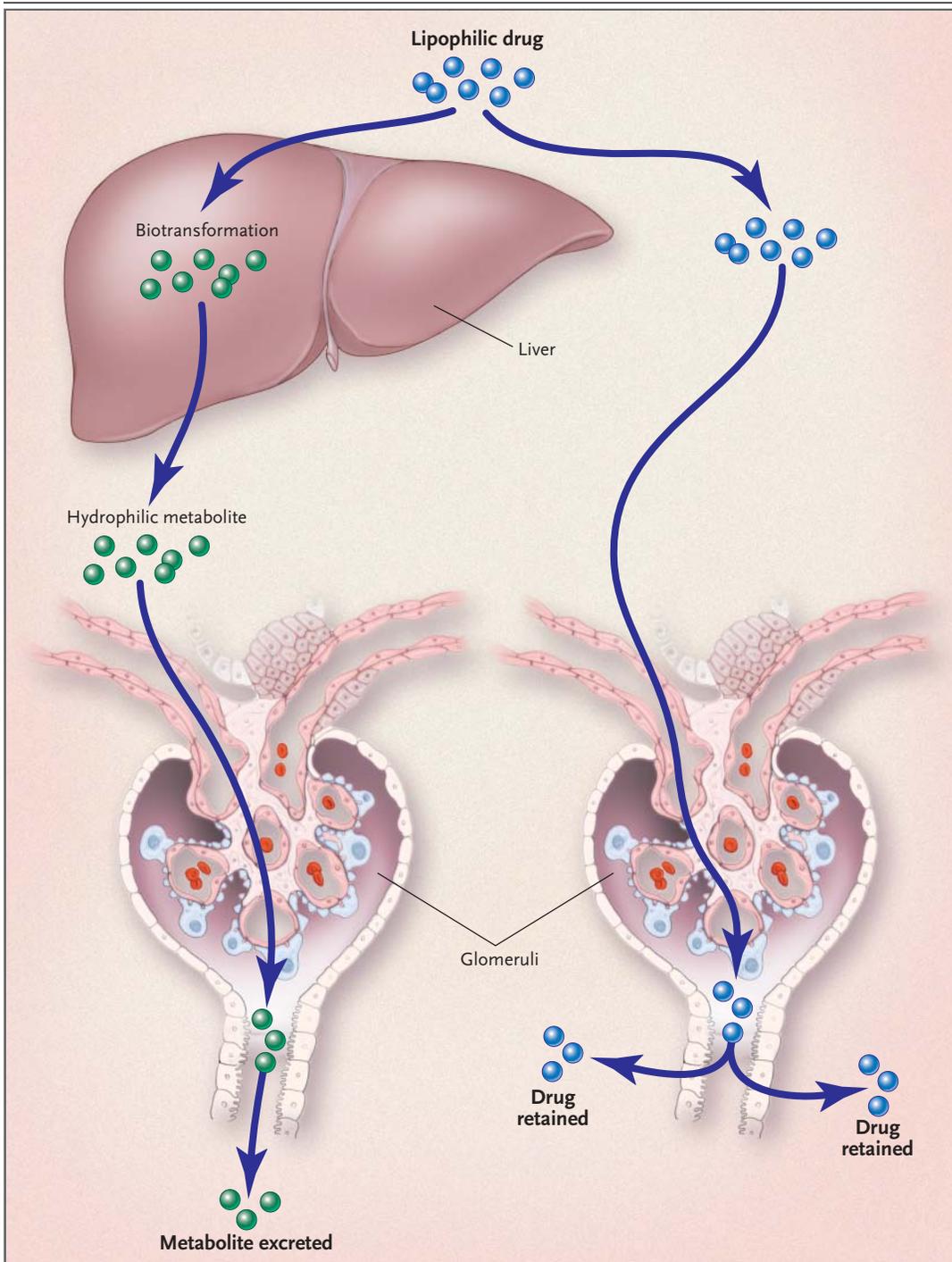
Figure 1. The Effect of Drug Metabolism on Excretion.

Lipophilic (or fat-soluble) drugs are metabolized to form relatively more hydrophilic (or water-soluble) metabolites than the parent drug, and these metabolites are thus more easily excreted.
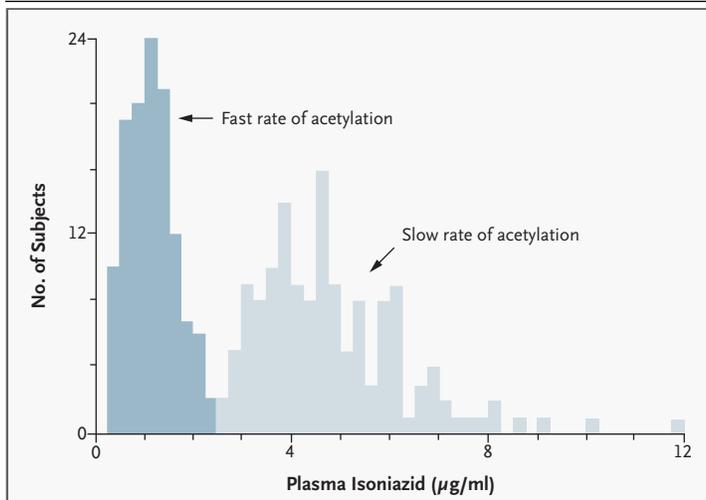
Figure 2. Pharmacogenetics of Acetylation.

Plasma isoniazid concentrations were measured in 267 subjects six hours after an oral dose. The bimodal distribution in the rate of acetylation is due to genetic polymorphisms within the *N*-acetyltransferase 2 gene. Modified from Price Evans et al.[10] with the permission of the publisher.
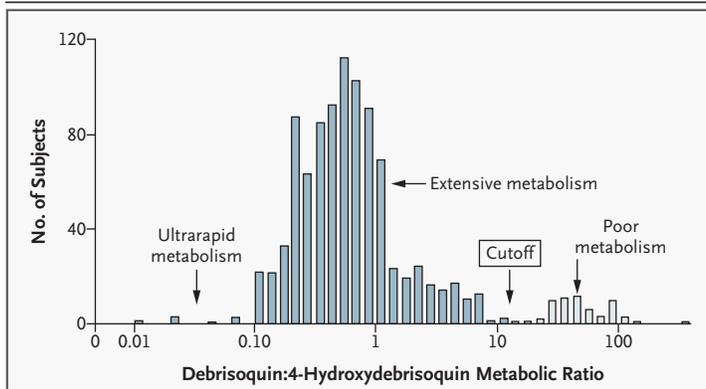

Figure 3. Pharmacogenetics of CYP2D6.

Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, are shown for 1011 Swedish subjects. The Cutoff box indicates the cutoff point between subjects with poor metabolism as a result of decreased or absent CYP2D6 activity and subjects with extensive metabolism. Modified from Bertilsson et al.[17] with the permission of the publisher.

anisms responsible for genetic polymorphisms, but also has created the possibility of high-throughput clinical tests that can be performed with DNA isolated from a blood sample, an approach that is being adapted for routine diagnostic use in clinical laboratories.

Application of molecular genetic techniques resulted in the cloning of a complementary DNA (cDNA) and the gene encoding CYP2D6.[19,20] Those advances, in turn, made it possible to characterize a series of genetic variants responsible for low levels of CYP2D6 activity or no activity, ranging from single-nucleotide polymorphisms that altered the amino acid sequence of the encoded protein to single-nucleotide polymorphisms that altered RNA splicing or even deletions of the *CYP2D6* gene.[21] More than 75 *CYP2D6* alleles have now been described (descriptions are available at http://www.imm.ki.se/cypalleles). In addition, some subjects with ultrarapid metabolism have been shown to have multiple copies of the *CYP2D6* gene.[18] Such subjects can have an inadequate therapeutic response to standard doses of the drugs metabolized by CYP2D6. Although the occurrence of multiple copies of the *CYP2D6* gene is relatively infrequent among northern Europeans, in East African populations, the allele frequency can be as high as 29 percent.[22] The effect of the number of copies of the *CYP2D6* gene — ranging from 0 to 13 — on the pharmacokinetics of the antidepressant drug nortriptyline is shown in Figure 4.[23] There could hardly be a more striking illustration of how genetics influences the metabolism of a drug.

The *CYP2D6* polymorphism represents an excellent example of both the potential clinical implications of pharmacogenetics and the process by which pharmacogenetic research led from the phenotype to an understanding of molecular mechanisms at the level of the genotype. Similar approaches were subsequently applied to other cytochrome P-450 isoforms, including 2C9, which metabolizes warfarin, losartan, and phenytoin; 2C19, which metabolizes omeprazole; and 3A5, which metabolizes a very large number of drugs.[24-26] We now know that many other phase I drug-metabolizing enzymes display genetic variation that can influence a person's response to a drug. Table 1 lists selected examples of clinically relevant pharmacogenetic variations involving phase I drug-metabolizing enzymes. In many cases, we also understand the molecular basis of inherited variation in the drug-metabolizing enzymes. For example, in the atypical butyrylcholinesterase variant responsible for striking decreases in the ability to catalyze the hydrolysis of succinylcholine, guanine is substituted for adenine at position 209 in the open reading frame of the gene, resulting in a change from aspartic acid to glycine at position 70 in the encoded protein.[42] A series of other variant alleles for bu-

tyrylcholinesterase that result in decreased enzyme activity have also been described.[41]

Another example of the pharmacogenetics of phase I drug metabolism involves metabolism of the antineoplastic agent fluorouracil. In the mid-1980s, fatal central nervous system toxicity developed in several patients after treatment with standard doses of fluorouracil.[39,40] The patients were shown to have an inherited deficiency of dihydropyrimidine dehydrogenase, an enzyme that metabolizes fluorouracil and endogenous pyrimidines. Subsequently, several variant alleles for the gene encoding dihydropyrimidine dehydrogenase were described that placed patients at risk for toxic effects when they were exposed to standard doses of fluorouracil.[43] The pharmacogenetics of dihydropyrimidine dehydrogenase and its effect on the metabolism of fluorouracil, as well as the pharmacogenetics of thiopurine drugs discussed below, serve to illustrate another general principle: pharmacogenetic variation in the response to drugs has been recognized most often for drugs with narrow therapeutic indexes — drugs for which differences between the toxic and therapeutic doses are relatively small. However, the same general principles would be expected to apply to all therapeutic agents, and the same research strategies that were used to identify common, clinically significant genetic variations in phase I pathways of drug metabolism have also been applied — with equal success — to reactions involving phase II drug metabolism.
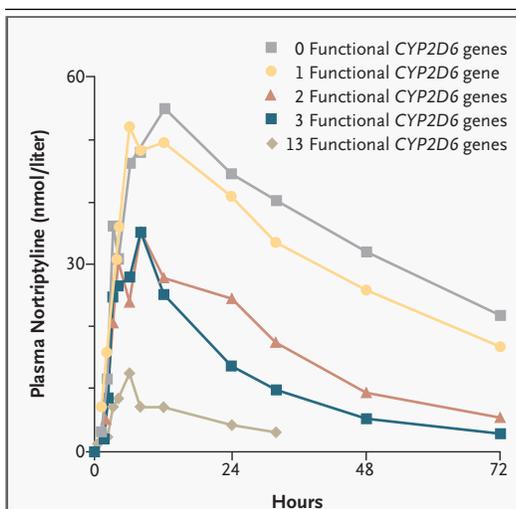

Figure 4. Pharmacogenetics of Nortriptyline.

Mean plasma concentrations of nortriptyline after a single 25-mg oral dose are shown in subjects with 0, 1, 2, 3, or 13 functional *CYP2D6* genes. Modified from Dalén et al.[23] with the permission of the publisher.

PHARMACOGENETICS OF PHASE II DRUG METABOLISM

The N-acetylation of isoniazid (Fig. 2) was an early example of inherited variation in phase II drug metabolism. Molecular cloning studies subsequently demonstrated that there are two N-acetyltransferase (NAT) genes in humans, NAT1 and NAT2.[44] The

---

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

| Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[16] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[36,37]
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous[38]	Fluorouracil[39,40]	Enhanced drug effect[39,40]
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans[41]	Succinylcholine[9,41]	Enhanced drug effect[9,41]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

common genetic polymorphism responsible for the pharmacogenetic variation in isoniazid metabolism illustrated in Figure 2 involved the NAT2 gene. That polymorphism, like those in the genes for many other drug-metabolizing enzymes, shows striking ethnic variation.[45] As a result, most East Asian subjects are rapid acetylators of isoniazid and other drugs metabolized by N-acetyltransferase 2.[46] Although the NAT2 genetic polymorphism was one of the earliest examples discovered of a pharmacogenetic variant in a phase II drug-metabolizing enzyme, it was a common genetic polymorphism involving another conjugating (i.e., phase II) enzyme that became one of the earliest clinically accepted pharmacogenetic tests.

Figure 5. Pharmacogenetics of Thiopurine *S*-Methyltransferase (TPMT) (Panel A) and the *TPMT* Gene (Panel B).

Panel A shows the level of TPMT activity in red cells among 298 randomly selected white adult blood donors. Presumed genotypes for the *TPMT* genetic polymorphism are also shown. TPMT^L and TPMT^H are alleles that result clinically in low levels and high levels of activity, respectively. These allele designations were used before the molecular basis for the polymorphism was understood. (Modified from Weinshilboum and Sladek[50] with the permission of the publisher.) Panel B shows the human *TPMT* gene. *TPMT*1* is the most common allele, and *TPMT*3A* is the most common variant allele among white subjects. The *TPMT*3A* allele is primarily responsible for the trimodal frequency distribution shown in Panel A. The two single-nucleotide polymorphisms in *TPMT*3A*, which are in strong linkage disequilibrium, as well as the resultant changes in encoded amino acids, are indicated.

The thiopurine drugs mercaptopurine and azathioprine — a prodrug that is converted to mercaptopurine in vivo — are purine antimetabolites used clinically as immunosuppressants and to treat neoplasias, such as acute lymphoblastic leukemia of childhood.[47] Thiopurines are metabolized in part by S-methylation catalyzed by the enzyme thiopurine S-methyltransferase (TPMT).[48,49] Approximately 20 years ago it was reported that white populations can be separated into three groups on the basis of the level of TPMT activity in their red cells and other tissues and that the level of activity was inherited in an autosomal codominant fashion (Fig. 5A).[50,51] Subsequently, it was shown that when persons who were homozygous for low levels of TPMT activity or for no activity (TPMT^L/TPMT^L) (Fig. 5A) received standard doses of thiopurines, they had greatly elevated concentrations of active metabolites, 6-thioguanine nucleotides, as well as a greatly increased risk of life-threatening, drug-induced myelosuppression.[52] As a result, the phenotypic test for the level of TPMT activity in red cells and, subsequently, DNA-based tests were among the first pharmacogenetic tests to be used in clinical practice. They are an example of the individualization of therapy on the basis of pharmacogenetic data. Patients with inherited low levels of TPMT activity can be treated with thiopurine drugs but only at greatly reduced doses, if drug-induced toxicity is to be avoided.[51] There is also evidence that in patients with very high levels of activity, the efficacy of thiopurine drugs is decreased,[53] presumably because the drugs are rapidly metabolized.

It is interesting to contrast the test used to determine the TPMT phenotype with that used originally to classify subjects as having either poor or extensive metabolism of CYP2D6. In the case of TPMT, a blood sample could be obtained and the enzymatic activity measured directly, whereas for CYP2D6 a probe drug had to be administered and a urine sample collected (Fig. 3). The fact that TPMT is expressed in an easily accessible cell — the red cell — facilitated the introduction of this pharmacogenetic test into clinical use. The availability of DNA-based tests means that the clinical application of pharmacogenetics could be greatly accelerated for a large number of genes that encode proteins important in drug response.

The TPMT gene has been cloned,[54] and the most common variant allele responsible for low levels of activity among white populations encodes a protein with two alterations in the amino acid sequence as a result of single-nucleotide polymorphisms
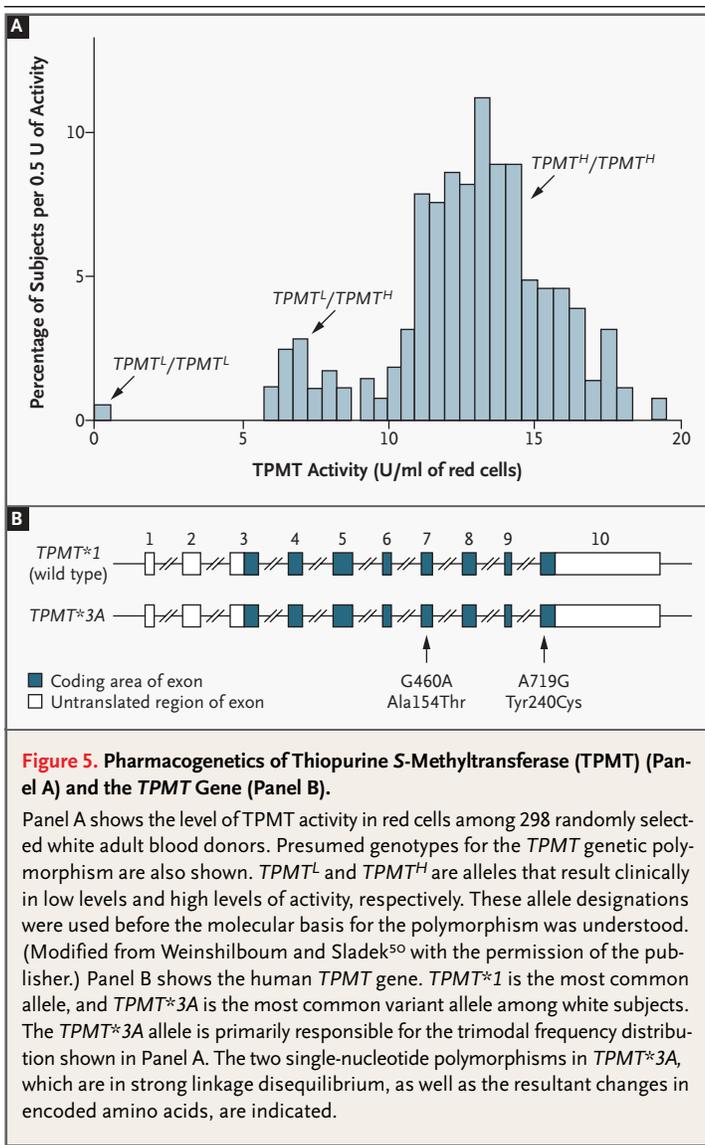
(Fig. 5B).[54,55] These sequence changes result in a striking reduction in the quantity of TPMT,[54] probably because the variant protein is degraded rapidly.[56] A series of less frequent TPMT variant alleles have also been described.[51] Finally, there are large differences in the types and frequencies of TPMT alleles among ethnic groups. For example, TPMT*3A, the most common allele responsible for very low levels of enzyme activity in whites, with a frequency of approximately 4 percent (Fig. 5B), has not been observed in China, Korea, or Japan.[57] Other examples of pharmacogenetic variation involving phase II pathways of drug metabolism are listed in Table 2.

Recurring themes in pharmacogenetics include the presence of a few relatively common variant alleles of genes encoding proteins important in drug response, a larger number of much less frequent variant alleles, and striking differences in the types and frequencies of alleles among different populations and ethnic groups. These generalizations, based primarily on studies of drug metabolism, are now being extended to include common genetic variations in other proteins that might alter the effects of drug transporters or targets.

Most drugs are metabolized by several different enzymes, can be transported by other types of proteins, and ultimately interact with one or more targets. If several steps in this type of pathway were to display genetic variation — that is, if the effects were polygenic — clear multimodal frequency distributions like those shown in Figures 2 and 3 would quickly be replaced by multiple overlapping distributions. Therefore, even if inheritance influenced the effect of a drug, the relatively simple, one-to-one relation observed for CYP2D6 and TPMT would not be obvious. Perhaps partly as a result of that fact, there are still relatively few examples of clinical tests based on pharmacogenetics. An additional factor responsible for the relatively slow translation of pharmacogenetic approaches into clinical practice — as mentioned previously — has been the frequent requirement for the administration of a probe drug in the diagnosis of many pharmacogenetic traits. DNA-based assays make it possible to obtain pharmacogenetic information on a large number of genes encoding relevant proteins. The range of functionally significant variations in DNA sequences in genes that influence the response to drugs is wide and includes single-nucleotide polymorphisms, small insertions and deletions, variable-number tandem repeats, gene deletions, and gene duplications. And although DNA-based tests can be used to detect sequence variations, the results of such tests will not necessarily account for all possible phenotypic variations. What they can potentially do quickly is make available large quantities of data on many genes that might contribute to variations in drug response.

FROM PHARMACOGENETICS TO PHARMACOGENOMICS

The convergence of pharmacogenetics and rapid advances in human genomics has resulted in pharmacogenomics, a term used here to mean the influence of DNA-sequence variation on the effect of a drug. With the completion of the Human Genome Project[66,67] and the ongoing annotation of its data, the time is rapidly approaching when the sequences of virtually all genes encoding enzymes

Table 2. Pharmacogenetics of Phase II Drug Metabolism.*			
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
N-Acetyltransferase 2	52% among white Americans[10] 17% of Japanese[58]	Isoniazid[10] Hydralazine[11] Procainamide[12]	Enhanced drug effect[13]
Uridine diphosphate–glucuronosyltransferase 1A1 (TATA-box polymorphism)	10.9% among whites[59] 4% of Chinese[60] 1% of Japanese[60]	Irinotecan[61] Bilirubin[62]	Enhanced drug effect[63] Gilbert's syndrome[62]
Thiopurine S-methyltransferase	Approximately 1 in 300 whites[50,57] Approximately 1 in 2500 Asians[57]	Mercaptopurine[51] Azathioprine	Enhanced drug effect (toxicity)[51-53]
Catechol O-methyltransferase	Approximately 25% of whites[51,64]	Levodopa[51,65]	Enhanced drug effect[51,65]

* Examples of genetically polymorphic phase II (conjugating) enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

that catalyze phase I and II drug metabolism will be known. The same will be true for genes that encode drug transporters, drug receptors, and other drug targets. As a result, the traditional phenotype-to-genotype pharmacogenetic-research paradigm described at the beginning of this article is reversing direction to create a complementary genotype-to-phenotype flow of information.

CONCLUSIONS

The convergence of advances in pharmacogenetics and human genomics means that physicians can now individualize therapy in the case of a few drugs. As our knowledge of genetic variations in proteins involved in the uptake, distribution, metabolism, and action of various drugs improves, our ability to test for that variation and, as a result, to select the best drug at the optimal dose for each patient should also increase.

REFERENCES

1. Kalow W. Pharmacogenetics: heredity and the response to drugs. Philadelphia: W.B. Saunders, 1962.

2. Price Evans DA. Genetic factors in drug therapy: clinical and molecular pharmacogenetics. Cambridge, England: Cambridge University Press, 1993.

3. Weber WW. Pharmacogenetics. New York: Oxford University Press, 1997.

4. Evans WE, McLeod HL. Pharmacogenomics — drug disposition, drug targets, and side effects. N Engl J Med 2003;348:538-49.

5. Wilkinson GR. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill, 2001:3-29.

6. Ross EM, Kenakin TP. Pharmacodynamics: mechanisms of drug action and the relationship between drug concentration and effect. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill, 2001:31-43.

7. Kalow W. The Pennsylvania State University College of Medicine 1990 Bernard B. Brodie Lecture: pharmacogenetics: past and future. Life Sci 1990;47:1385-97.

8. Kalow W, Gunn DR. Some statistical data on atypical cholinesterase of human serum. Ann Hum Genet 1959;23:239-50.

9. *Idem.* The relation between dose of succinylcholine and duration of apnea in man. J Pharmacol Exp Ther 1957;120:203-14.

10. Price Evans DA, Manley KA, McKusick VA. Genetic control of isoniazid metabolism in man. BMJ 1960;2:485-91.

11. Timbrell JA, Harland SJ, Facchini V. Polymorphic acetylation of hydralazine. Clin Pharmacol Ther 1980;28:350-5.

12. Reidenberg MM, Drayer DE, Levy M, Warner H. Polymorphic acetylation of procainamide in man. Clin Pharmacol Ther 1975;17:722-30.

13. Drayer DE, Reidenberg MM. Clinical consequences of polymorphic acetylation of basic drugs. Clin Pharmacol Ther 1977;22:251-8.

14. Kroemer HK, Eichelbaum M. "It's the genes, stupid": molecular bases and clinical consequences of genetic cytochrome P450 2D6 polymorphism. Life Sci 1995;56:2285-98.

15. Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet 1977;2:584-6.

16. Eichelbaum M, Spannbrucker N, Steincke B, Dengler HJ. Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. Eur J Clin Pharmacol 1979;16:183-7.

17. Bertilsson L, Lou YQ, Du YL, et al. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and S-mephenytoin. Clin Pharmacol Ther 1992;51:388-97. [Erratum, Clin Pharmacol Ther 1994;55:648.]

18. Johansson I, Lundqvist E, Bertilsson L, Dahl ML, Sjoqvist F, Ingelman-Sundberg M. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. Proc Natl Acad Sci U S A 1993;90:11825-9.

19. Gonzalez FJ, Vilbois F, Hardwick JP, et al. Human debrisoquine 4-hydroxylase (P450IID1): cDNA and deduced amino acid sequence and assignment of the CYP2D locus of chromosome 22. Genomics 1988;2:174-9.

20. Kimura S, Umeno M, Skoda R, Meyer UA, Gonzalez FJ. The human debrisoquine 4-hydroxylase (CYP2D) locus: sequence and identification of the polymorphic CYP2D6 gene, a related gene and a pseudogene. Am J Hum Genet 1989;45:889-904.

21. Ingelman-Sundberg M, Evans WE. Unravelling the functional genomics of the human CYP2D6 gene locus. Pharmacogenetics 2001;11:553-4.

22. Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. J Pharmacol Exp Ther 1996;278:441-6.

23. Dalén P, Dahl ML, Ruiz MLB, Nordin J, Bertilsson L. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444-52.

24. Stubbins MJ, Harris LW, Smith G, Tarbit MH, Wolf CR. Genetic analysis of the human cytochrome P450 CYP2C9 locus. Pharmacogenetics 1996;6:429-39.

25. de Morais SMF, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem 1994;269:15419-22.

26. Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001;27:383-91.

27. Mortimer O, Persson K, Ladona MG, et al. Polymorphic formation of morphine from codeine in poor and extensive metabolizers of dextromethorphan: relationship to the presence of immunoidentified cytochrome P-450IID1. Clin Pharmacol Ther 1990;47:27-35.

28. Sindrup SH, Brøsen K. The pharmacogenetics of codeine hypoalgesia. Pharmacogenetics 1995;5:335-46.

29. Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999;353:717-9.

30. Loebstein R, Yonath H, Peleg D, et al. Interindividual variability in sensitivity to warfarin — nature or nurture? Clin Pharmacol Ther 2001;70:159-64.

31. van der Weide J, Steijns LSW, van Weelden MJM, de Haan K. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. Pharmacogenetics 2001;11:287-91.

32. Brandolese R, Scordo MG, Spina E, Gusella M, Padrini R. Severe phenytoin intoxication in a subject homozygous for CYP2C9*3. Clin Pharmacol Ther 2001;70: 391-4.

33. Nakamura K, Goto F, Ray WA, et al. Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. Clin Pharmacol Ther 1985; 38:402-8.

34. Balian J, Sukhova N, Harris JW, et al. The hydroxylation of omeprazole correlates with *S*-mephenytoin metabolism: a population study. Clin Pharmacol Ther 1995;57:662-9.

35. Tybring G, Böttiger Y, Widén J, Bertilsson L. Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. Clin Pharmacol Ther 1997;62:129-37.

36. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rate for *Helicobacter pylori* infection and peptic ulcer. Ann Intern Med 1998;129:1027-30.

37. Tanigawara Y, Aoyama N, Kita T, et al. *CYP2C19* genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. Clin Pharmacol Ther 1999;66:528-34.

38. Raida M, Schwabe W, Hausler P, et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5′-splice donor site of intron 14 in patients with severe 5-fluorouracil (5-FU)-related toxicity compared with controls. Clin Cancer Res 2001;7:2832-9.

39. Tuchman M, Stoeckeler JS, Kiang DT, O'Dea RF, Ramnaraine ML, Mirkin BL. Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. N Engl J Med 1985;313:245-9.

40. Diasio RB, Beavers TL, Carpenter JT. Familial deficiency of dihydropyrimidine dehydrogenase: biochemical basis for familial pyrimidinemia and severe 5-fluorouracil-induced toxicity. J Clin Invest 1988;81:47-51.

41. Lockridge O. Genetic variants of human butyrylcholinesterase influence the metabolism of the muscle relaxant succinylcholine. In: Kalow W, ed. Pharmacogenetics of drug metabolism. International encyclopedia of pharmacology and therapeutics. New York: Pergamon Press, 1992:15-50.

42. McGuire MC, Nogueira CP, Bartels CF, et al. Identification of the structural mutation responsible for the dibucaine-resistant (atypical) variant form of human serum cholinesterase. Proc Natl Acad Sci U S A 1989; 86:953-7.

43. McLeod HL, Collie-Duguid ESR, Vreken P, et al. Nomenclature for human DPYD alleles. Pharmacogenetics 1998;8:455-9.

44. Blum M, Grant DM, McBride W, Heim M, Meyer UA. Human arylamine N-acetyltransferase genes: isolation, chromosomal localization, and functional expression. DNA Cell Biol 1990;9:193-203.

45. Lin HJ, Han C-Y, Lin BK, Hardy S. Slow acetylator mutations in the human polymorphic N-acetyltransferase gene in 786 Asians, blacks, Hispanics, and whites: application to metabolic epidemiology. Am J Hum Genet 1993;52:827-34.

46. Price Evans DA. N-acetyltransferase in pharmacogenetics of drug metabolism. In: Kalow W, ed. Pharmacogenetics of drug metabolism. International encyclopedia of pharmacology and therapeutics. New York: Pergamon Press, 1992:43:95-178.

47. Lennard L. The clinical pharmacology of 6-mercaptopurine. Eur J Clin Pharmacol 1992;43:329-39.

48. Remy CN. Metabolism of thiopyrimidines and thiopurines: *S*-methylation with *S*-adenosylmethionine transmethylase and catabolism in mammalian tissues. J Biol Chem 1963;238:1078-84.

49. Woodson LC, Weinshilboum RM. Human kidney thiopurine methyltransferase: purification and biochemical properties. Biochem Pharmacol 1983;32:819-26.

50. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am J Hum Genet 1980; 32:651-62.

51. Weinshilboum RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol 1999;39:19-52.

52. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. Clin Pharmacol Ther 1989;46:149-54.

53. Lennard L, Lilleyman JS, Van Loon J, Weinshilboum RM. Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. Lancet 1990;336:225-9.

54. Szumlanski C, Otterness D, Her C, et al. Thiopurine methyltransferase pharmacogenetics: human gene cloning and characterization of a common polymorphism. DNA Cell Biol 1996;15:17-30.

55. Tai H-L, Krynetski EY, Yates CR, et al. Thiopurine S-methyltransferase deficiency: two nucleotide transitions define the most prevalent mutant allele associated with loss of catalytic activity in Caucasians. Am J Hum Genet 1996;58:694-702.

56. Tai H-L, Krynetski EY, Schuetz EG, Yanishevski Y, Evans WE. Enhanced proteolysis of thiopurine *S*-methyltransferase (TPMT) encoded by mutant alleles in humans (TPMT*3A, TPMT*2): mechanisms for the genetic polymorphism of TPMT activity. Proc Natl Acad Sci U S A 1997;94:6444-9.

57. Collie-Duguid ESR, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. Pharmacogenetics 1999;9:37-42.

58. Dufour AP, Knight RA, Harris HW. Genetics of isoniazid metabolism in Caucasian, Negro, and Japanese populations. Science 1964;145:391.

59. Lampe JW, Bigler J, Horner NK, Potter JD. UDP-glucuronosyltransferase (UGT1A1*28 and UGT1A6*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. Pharmacogenetics 1999;9:341-9.

60. Hall D, Ybazeta G, Destro-Bisol G, Petzl-Erler ML, Di Rienzo A. Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. Pharmacogenetics 1999;9:591-9.

61. Iyer L, Hall D, Das S, et al. Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. Clin Pharmacol Ther 1999;65:576-82.

62. Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995;333:1171-5.

63. Iyer L, Das S, Janisch L, et al. *UGT1A1*28* polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenetics J 2002;2:43-7.

64. Weinshilboum RM, Raymond FA. Inheritance of low erythrocyte catechol-o-methyltransferase activity in man. Am J Hum Genet 1977;29:125-35.

65. Reilly DK, Rivera-Calimlim L, Van Dyke D. Catechol-O-methyltransferase activity: a determinant of levodopa response. Clin Pharmacol Ther 1980;28:278-86.

66. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001;409:860-921. [Errata, Nature 2001;411:720, 412:565.]

67. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science 2001;291:1304-51. [Erratum, Science 2001;292:1838.]

Copyright © 2003 Massachusetts Medical Society.