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PHARMACOGENOMICS AND PERSONALIZED THERAPEUTICS IN PSYCHIATRY

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The advances in molecular medicine are taking place at a hitherto unprecedented pace. Genetics has come of age and will greatly influence the future of health care and therapeutics in the twenty-first century, in much the same way the breakthroughs in quantum physics and chemistry shaped science and society during the early phases of the twentieth century.

The field of pharmacogenetics was introduced more than 40 years ago to emphasize the role of heredity in person-to-person differences in drug response (1,2). The focus of pharmacogenetic investigations has traditionally been unusual and extreme drug responses resulting from a single gene effect. Pharmacogenomics is a recently introduced concept that attempts to explain the hereditary basis of both monogenic as well as subtler and continuous variations in drug responses that are under multigenic control (3). Although the two terms are often used interchangeably, the scope of pharmacogenomic investigations follows a genome-wide approach and also aims to identify novel biological targets for drug discovery, with use of the new affordable high-throughput molecular genetic technologies (4). In theory, pharmacogenomics can assist in clinical decision making to choose the most appropriate medication and dose titration regimen for individual patients. Moreover, the principles of pharmacogenomics are not limited to therapeutics. They can be applied to understand the hereditary basis of differences in sensitivity or resistance to any foreign chemical (xenobiotics) or environmental factor including foodstuffs, pesticides, infectious diseases, and ionizing radiation (5–7).

The Human Genome Project has already provided a draft nucleotide sequence of the human genome by mid-2000 and the nearly complete sequence is projected to be available by 2003. In addition, nucleotide sequence variations among individuals, populations, and species will be available in the near future. It is clear that these advances will soon lead to identification of many genes causing common complex diseases, thereby creating numerous new potential drug targets. This will also present a bioinformatics and data analysis challenge for lead optimization among numerous new chemical entities (NCE) directed to such disease targets for therapeutic purposes. Pharmacogenomics is a hybrid research field that bridges the knowledge gained from the Human Genome Project with existing principles of population genetics, pharmacokinetics, pharmacodynamics, cell physiology, proteomics, and bioinformatics. It is expected that pharmacogenomics will importantly contribute to development of guidelines for rational and personalized drug treatment; it should also expedite the drug discovery, development, and approval process in the pharmaceutical industry (8).

The purpose of this chapter is to introduce pharmacogenomics to those from a clinical psychiatry perspective, and discuss the future research challenges for those who may have prior experience in the field.

HISTORICAL OVERVIEW AND CONCEPTUAL FRAMEWORK FOR PERSONALIZED THERAPEUTICS

The marked interindividual variability in psychotropic drug effects was recognized long ago (9,10). For example, the

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same dose of an antidepressant medication may cause toxicity, efficacious treatment, lack of efficacy, or qualitatively different drug effects among patients and populations (11). Understanding the sources of such variability in dose–response relationships is central to individualized dosage and choice of drugs for therapeutic purposes (12). Interestingly, it has been a commonly held viewpoint that genetics is important mainly for the permanent characteristics of an individual (e.g., stature) or predisposition to certain diseases, rather than variations in drug effects (13). In 1932, Snyder documented one of the first known interactions between heredity and response to xenobiotics: the ability to sense the bitter taste of phenylthiourea, which is under strong genetic control (14). In 1962 Werner Kalow published the first monograph on pharmacogenetics (1). Some argue that the field of pharmacogenetic inquiry dates as early as 510 BC, when Pythagorus in Croton, southern Italy, warned about the " . . . dangers of some, but not other, individuals who eat the fava bean" (5). The molecular basis of this historic observation was later documented to be hemolytic anemia owing to glucose-6-phosphate dehydrogenase deficiency.

The interest in personalized therapeutics was further fueled by the thalidomide disaster in 1960s. Subsequent observational studies found that drug–drug interactions, and hepatic and renal insufficiency importantly contribute to the risk for adverse drug reactions (15). A series of studies in monozygotic and dizygotic twins firmly established that genetic factors play an important role in metabolism of many drugs, and not only in a few cases of unusual adverse

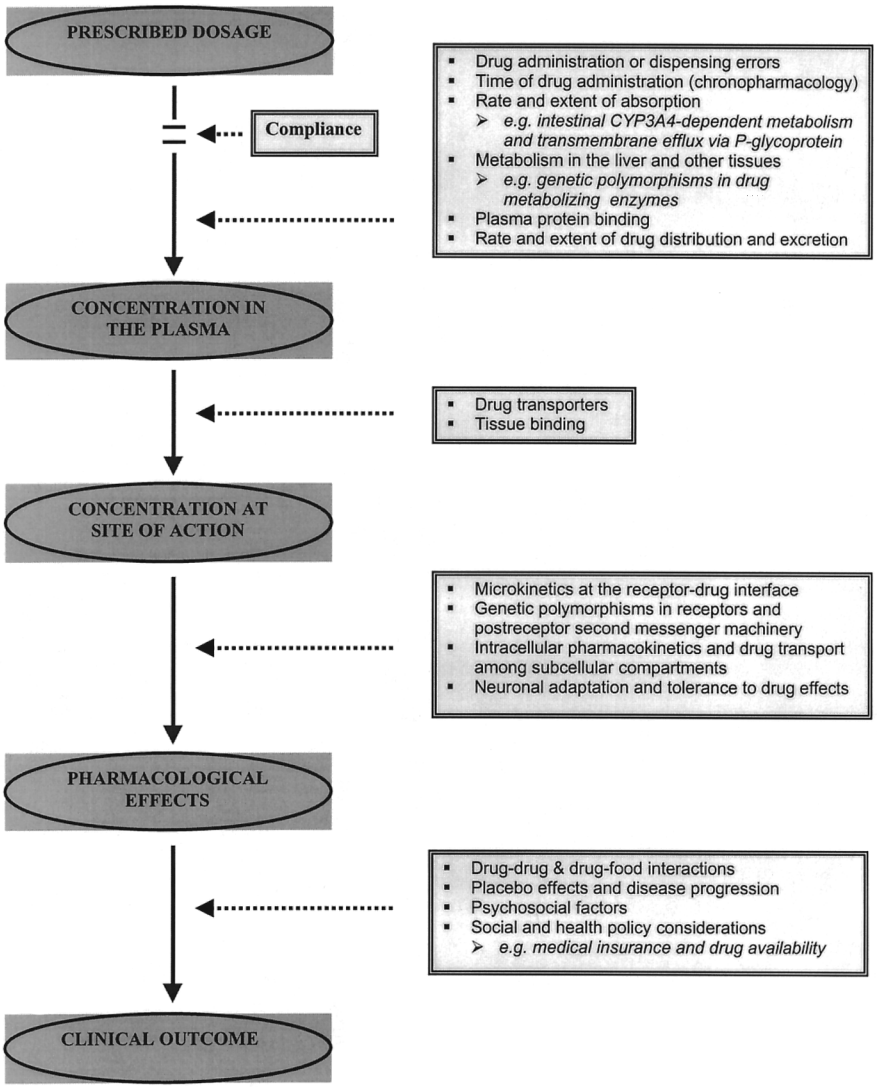

FIGURE 37.1. Pharmacological cascade describing the dose: clinical outcome relationship. Modified from Koch-Weser J. Drug therapy. Serum drug concentrations as therapeutic guides. *N Engl J Med* 1972;287:227–231.

drug reactions (16). This led to the publication of systematic guidelines on individualization of drug therapy by the American College of Physicians, based on genetic, environmental, and disease-related determinants of person-to-person differences in dose–effect relationships (17).

The pharmacologic drug response is a complex trait and is likely under polygenic control, rather than simple monogenic regulation (18). However, in comparison to disease-related complex traits, there is a well-established theoretic working model describing the relationship between the prescribed drug dosage and clinical drug effects (19). The conceptual framework developed by the seminal works of Sheiner and others allows one to target candidate genes with potential mechanistic relevance to partition the variability in any drug effect into pharmacokinetic and pharmacodynamic components (Fig. 37.1) (20–25).

The term pharmacokinetics describes the "drug concentration versus time" relationships in an organism by mathematical formulations of drug absorption from the site of administration, distribution, and elimination by metabolism and/or excretion (25). The pharmacodynamics explains the "drug concentration versus response" relationships and the related biological covariates (e.g., receptors, second messenger systems) (25). At present, pharmacogenomics is extending the early pharmacogenetic studies of drug metabolism to a broader context, to dissect the genetic control at multiple levels of the pharmacokinetic and pharmacodynamic pharmacologic cascade, from drug absorption and transport to drug–receptor interface and beyond. The progress made by pharmacogenomics, in many ways, is akin to developments in the computer industry. The potential benefits of high speed and efficient computing was self-evident early in the days of cumbersome mainframe computers, but it was not until the development of low-cost and proficient microcomputers that computerized information processing could be applied in daily life (analogous to contemporary ultrahigh throughput microarray genotyping technologies).

HUMAN GENETIC VARIATION AND SINGLE NUCLEOTIDE POLYMORPHISMS

The biallelic single nucleotide polymorphisms (SNPs) represent the most common DNA sequence variation in the human genome. It is thought that the complete human sequence including the coding regions, introns, and promoters will contain approximately one million SNPs (26). SNPs often result in predictable changes in amino acid sequence and contribute to diversity in protein function. SNPs are valuable biomarkers to elucidate the genetic basis of common complex diseases and pharmacologic traits. In the near term, the new genomic technologies will allow large-scale genetic association studies between numerous SNPs and drug response phenotype(s) in large samples of patients during routine drug treatment and clinical trials.

A pharmacogenetic polymorphism refers to a " . . . Mendelian or monogenic trait that exists in the population in at least two phenotypes (and presumably at least two genotypes), neither of which is rare; that is, neither of which occurs with a frequency of less than 1 to 2% . . . " (27). The definition of the minimum frequency threshold (i.e., 1% to 2%) is arbitrary and aims to emphasize that pharmacogenetic polymorphisms are *not* rare and different from those owing to recurrent spontaneous mutations occurring at much lower frequencies. A characteristic feature of pharmacogenetic polymorphisms is that they are usually biologically silent and do not present an evolutionary disadvantage or result in disease. This allows the maintenance of the less frequent phenotype at or above the 1% to 2% frequency level. Their clinical manifestations occur only when exposed to drugs or other xenobiotics, which target the polymorphic gene products.

Evident in the definition of pharmacogenetic polymorphism described in the preceding is the emphasis on phenotype (14). Alternative definitions of pharmacogenetic polymorphisms based on allele frequency also have been suggested (28,29). For example, Harris (1980) proposed that a genetic polymorphism occurs if the " . . . commonest identifiable allele (p) has a frequency no greater than 0.99 . . . " (29). It was pointed out earlier that if the goal of pharmacogenetic studies is to investigate the clinical relevance of pharmacogenetic polymorphisms, phenotype-based definition of polymorphisms might be more applicable (28). On the other hand, if the goal is to use genetic polymorphisms as anthropological tools to study the evolution of the species and differences in response to xenobiotics between populations, a definition incorporating both allelic variations and phenotype may be more appropriate to allow understanding at a molecular and mechanistic level (28).

GENETIC VARIABILITY IN DRUG METABOLISM: CONTRIBUTION TO PHARMACOKINETIC VARIABILITY

Drug metabolism is one of the pivotal factors, which contribute to variability in pharmacokinetics. Drug metabolism is generally divided into two phases. Phase 1 reactions involve oxidative, reductive, and hydrolytic reactions, which unmask or introduce a functional group (e.g., a hydroxyl-moiety) to the parent compound. This often results in an increase in polarity of the drug. Phase 2 reactions involve conjugation (e.g., with glucuronic acid) of the metabolite produced in phase 1 reactions, or the parent compound, to more hydrophilic metabolites (30). Although drug metabolism is necessary for the elimination of lipophilic drugs (e.g., psychotropics), it may also be crucial for activation of prodrugs (e.g., codeine).

Phase 1 reactions are mediated, to a large extent, by the CYP enzymes that are mostly found attached to the smooth endoplasmic reticulum of the hepatocytes and other drug metabolizing cells (e.g., enterocyte in the gut) (31). A recent analysis of over 300 drugs from diverse therapeutic classes such as psychotropics, analgesics, and anti-infectious agents found that 56% of them primarily depend on CYPs for their metabolic clearance (32). Among CYPs, the largest contributions are made by CYP3A4 (50%), CYP2D6 (20%), CYP2C9, and CYP2C19 (15%) (32). Some of the drug metabolizing enzymes (e.g., CYP1A2 and CYP2D6) are also expressed in the brain and may potentially play a role in local disposition of psychotropics at the site of action (33,34).

CYTOCHROME P450 2D6 GENETIC POLYMORPHISM: A COMMON AND CLASSICAL EXAMPLE OF A MONOGENIC VARIATION IN DRUG METABOLISM

CYP2D6 genetic polymorphism is one of the most intensively studied autosomal recessive monogenic defects in drug metabolism. Many psychotropics, including most typical (e.g., perphenazine) and some atypical antipsychotics (e.g., risperidone), tricyclic antidepressants (e.g., nortriptyline), drugs of abuse, some of the serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine), and codeine are metabolized by CYP2D6 (35–37).

Among Whites, approximately 7% of the population are poor metabolizers (PMs), whereas the rest are extensive metabolizers (EMs) for CYP2D6 substrates (35). The prevalence of PMs and the distribution of enzyme activity appear to be fairly consistent across the Western European and North American Whites. On the other hand, the frequency and type of *CYP2D6* alleles vary considerably among different ethnic groups. In Asians, the prevalence of PMs is only 1%, owing to almost complete absence of the nonfunctional alleles (e.g., *CYP2D6*4*) found in Whites (35). However, an often overlooked point in comparisons of pharmacogenetic polymorphisms between populations (e.g., Asians *versus* Whites) is that the key dependent variable is not only the prevalence of PMs but also the distribution of enzyme activity *within* EMs (36). Asian EMs (i.e., 99% of the population) display a significant shift in the distribution of CYP2D6 activity toward lower levels. The molecular basis of a lower CYP2D6 activity in Asian EMs is owing to a $C^{188} \rightarrow T$ base change in exon 1 which leads to $Pro^{34} \rightarrow Ser$ amino acid substitution in a highly conserved region (Pro-Pro-Gly-Pro) characteristic of CYP1 and CYP2 families (37). This allele was named *CYP2D6*10* (51% allele frequency in Chinese) and leads to a 10-fold decrease in activity *in vivo* (35). Thus, there may be discrete interindividual differences in disposition and therapeutic/adverse effects of psychotropics *within* Asians, depending on the gene-dose for the *CYP2D6*10* allele.

Another novel allele with reduced catalytic function, *CYP2D6*17,* occurs at high frequency in many black African populations and African-Americans. However, there appears to be considerable heterogeneity in the *CYP2D6* locus in Black populations. For example, in Ethiopia, only 1.8% were PMs of debrisoquine, 16% carried the *CYP2D6*10B* allele characteristic of Asian populations, and the *CYP2D6*17* was present in 18% of the subjects (38). Importantly, 29% of the Ethiopians carried alleles with duplicated and multiduplicated CYP2D6 genes associated with ultrarapid metabolism of substrates (38). Also, a high percentage of gene duplication and ultrarapid metabolism was found in Saudi Arabia and Spain, presumably owing to the genetic admixture during the earlier Islamic migration originating from some of the North African populations with ultrarapid CYP2D6 activity (36,37). The clinical significance of reduced catalytic function associated with the *CYP2D6*17* allele requires further research in patients with African ancestry.

At present, more than 50 *CYP2D6* alleles were described that encode an enzyme with inactive, decreased, increased, or normal catalytic function. The number of functional *CYP2D6* genes correlates with drug and metabolite concentrations in the plasma, as aptly documented using nortriptyline as a model substrate (Fig. 37.2) (39). In general, PMs are at risk for drug toxicity on treatment with medications predominantly inactivated by metabolism via CYP2D6. On the other hand, in prodrugs, which need to be converted to their active form by CYP2D6, opposite clinical consequences may occur in PMs. For example, codeine does not produce analgesic effects in PMs or after treatment of EMs with CYP2D6 inhibitors such as quinidine. Among EMs, those with duplicated or multiduplicated CYP2D6 genes and ultrarapid metabolism may develop subtherapeutic plasma concentrations and inadequate clinical response (40). Although high doses would be necessary in such patients, an alternative strategy would be to use low subtherapeutic doses of the CYP2D6 inhibitor quinidine, especially for drugs with high acquisition costs, to attain therapeutic plasma concentrations (41). Overall, routine genotyping for *CYP2D6* may be useful to avoid drug toxicity in PMs, to ascertain the pharmacokinetic mechanism of resistance to some psychotropics, as well as for differential diagnosis of noncompliance versus ultrarapid CYP2D6 activity. In addition, the markedly increased metabolite formation in patients with multiduplicated *CYP2D6* genes may potentially lead to qualitatively different and unexpected drug effects and toxicity (40).

It is noteworthy that CYP2D6 with identical pharmacologic and molecular properties was identified in microsomal fractions in the brain. Hence, CYP2D6 may potentially contribute to local clearance of psychotropics at the site of action (42). Moreover, CYP2D6 in the brain is functionally associated with the dopamine transporter and shares similar-

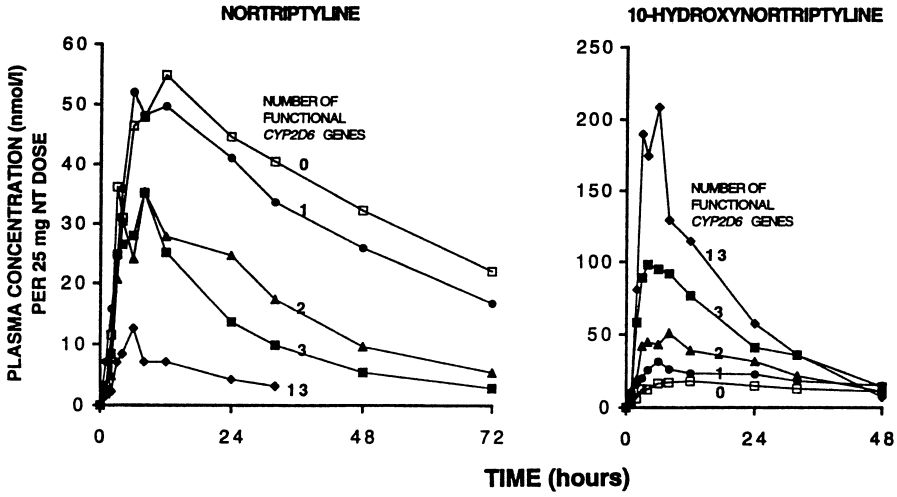

FIGURE 37.2. Average plasma concentrations of nortriptyline and 10-hydroxynortriptyline after a 25-mg single oral dose in White healthy volunteers with 0, 1, 2, 3, and 13 functional copies of the CYP2D6 gene. Note that the concentration of nortriptyline and its metabolite 10-hydroxynortriptyline are inversely affected by the number of functional CYP2D6 gene. Reprinted with permission from Dalén P, Dahl ML, Ruiz ML et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther* 1998;63:444–452.

ities in substrates and inhibitors (e.g., d-amphetamine), suggesting a role in dopaminergic neurotransmission (42). Differences in personality traits between EMs and PMs were noted in both Swedish and Spanish healthy White subjects, also suggesting that there may be an endogenous substrate for CYP2D6 in the brain (42).

The common polymorphic drug metabolizing enzymes in humans and their major variant alleles are presented in Table 37.1 (37). A worldwide web page with detailed descriptions of new alleles, nomenclature and useful references can be found at *(http://www.imm.ki.se/CYPalleles/).*

CYP3A4: A NONPOLYMORPHIC VARIATION IN DRUG METABOLISM

The term "polymorphic metabolism" is often perceived as an alarming indication of marked variability in drug disposition. Although this assertion is correct to a certain extent, it does not imply that a nonpolymorphic drug-metabolizing enzyme is associated with reduced variability. For example, CYP3A4 is the most abundant CYP isoform in the adult human liver with large interindividual variability in its expression. *In vivo,* CYP3A4 activity displays at least 20-

TABLE 37.1. HUMAN POLYMORPHIC CYTOCHROME P450 ENZYMES AND THE GLOBAL DISTRIBUTION OF THEIR MAJOR VARIANT ALLELES

				Allele Frequencies (%)			
Enzyme	Major Variant Alleles	Mutation	Consequences for Enzyme Function	Caucasians	Asians	Black Africans	Ethiopians and Saudi Arabians
CYP2A6	*CYP2A6*2*	Leu160His	Inactive enzyme	1–3	0	ND	ND
	*CYP2A6*del*	Gene deletion	No enzyme	1	15	ND	ND
CYP2C9	*CYP2C9*2*	Arg144Cys	Reduced affinity for P450 oxidoreductase	8–13	0	ND	ND
	*CYP2C9*3*	Ile359Leu	Altered substrate specificity	6–9	2–3	ND	ND
CYP2C19	*CYP2C19*2*	Aberrant splice site	Inactive enzyme	13	23–32	13	14–15
	*CYP2C19*3*	Premature stop codon	Inactive enzyme	0	6–10	ND	0–2
CYP2D6	*CYP2D6*2xN*	Gene duplication or multiduplication	Increased enzyme activity	1–5	0–2	2	10–16
	*CYP2D6*4*	Defective splicing	Inactive enzyme	12–21	1	2	1–4
	*CYP2D6*5*	Gene deletion	No enzyme	2–7	6	4	1–3
	*CYP2D6*10*	Pro34Ser, Ser486Thr	Unstable enzyme	1–2	51	6	3–9
	*CYP2D6*17*	Thr107Ile, Arg296Cys, Ser486Thr	Reduced affinity for substrates	0	ND	34	3–9

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ND, not determined.

fold difference in the population (43). Yet, the distribution of CYP3A4 catalytic activity is unimodal and nonpolymorphic in many populations.

CYP3A4 contributes to disposition of more than 60 frequently prescribed therapeutic agents with diverse chemical structures including antilipidemics, benzodiazepines, HIV protease inhibitors, immunosuppressants, and macrolide antibiotics (43,44). CYP3A4 also plays an important role for the metabolism of endogenous steroids (e.g., testosterone) as well as activation of dietary mycotoxins (e.g., aflatoxin B1) (43). The prediction of CYP3A4-mediated drug metabolism is complicated by the presence of at least two distinct pools of the CYP3A4 protein, in the liver and intestine, whose expressions appear to be regulated independently. The appreciation of marked variability in CYP3A4 activity is critical for individualized treatment with CYP3A4 substrates, to forecast drug–drug interactions mediated by CYP3A4, and to identify the factors predisposing to long-term toxicity (e.g., prostate and liver cancer) associated with variable metabolism of steroid hormones and procarcinogens (44).

CYP3A4 expression can be markedly induced *in vivo* during chronic treatment with drugs such as the antibiotic rifampicin, anticonvulsant carbamazepine, and glucocorticoid dexamethasone (43). Conversely, CYP3A4 catalytic activity can be inhibited potently by commonly used drugs including the azole antifungal agents (e.g., ketoconazole) and the macrolide antibiotics (e.g., erythromycin), or by foodstuffs such as grapefruit juice (44). For example, excessive sedation or psychomotor impairment can occur after oral administration of benzodiazepines with a low bioavailability (e.g., triazolam) or some nonbenzodiazepine (e.g., buspirone) hypnosedatives together with grapefruit juice (44). Many patients with a mental health problem also use nonpsychotropic medications. In such cases, clinically significant hypotension may be observed during treatment with dihydropyridine calcium channel antagonists (e.g., nifedipine) and CYP3A4 inhibitors.

Studies in monozygotic and dizygotic twins indicate a high heritability ($H_2 = 0.88$) of CYP3A4 activity (45); however, there has been relatively little progress in identification of the molecular genetic underpinnings of heterogeneity in *CYP3A4* expression. Recently, a novel allele, *CYP3A4*2,* causing a Ser222Pro change was found in Whites at a frequency of 2.7%, but this allele was absent in Black and Chinese subjects (46). The *CYP3A4*2* displays a substrate-dependent diminished metabolic clearance; for instance, nifedipine (but not testosterone) intrinsic clearance is impaired (46). Because functional polymorphisms in the promoter or the coding region of CYP3A4 do not appear to be very common, it is likely that CYP3A4 activity represents a complex trait regulated by multiple interacting genetic loci in the genome (47).

GENETIC VARIABILITY IN RECEPTORS AND DRUG TRANSPORTERS: CONTRIBUTION TO PHARMACODYNAMIC VARIABILITY

Historically, the pharmacogenetic factors related to drug efficacy and safety were mainly studied in the context of drug metabolism (48). In the past decade, the increasing application of mathematical models for "concentration *versus* effect" relationships during routine drug development clearly documented the marked interindividual variability in pharmacodynamics (23). It is estimated that approximately 30,000 proteins with diverse structures are expressed in the human brain, many of which may serve as potential drug targets (49). Recent studies of SNPs in genes relevant for psychotropic pharmacodynamics indicate that human genetic variation in drug receptors and transporters may significantly contribute to overall variance in response to drugs.

Dopamine D3 receptor *(DRD3)* gene is expressed in the basal ganglia and is thought to play a role in locomotion. Three independent studies found that the Ser9Gly polymorphism in the N-terminal extracellular domain of the DRD3 is associated with an increased propensity to develop tardive dyskinesia in patients treated with typical antipsychotics (Fig. 37.3) (50–52). Pharmacogenetic polymorphisms in the dopamine D4 receptor *(DRD4)* gene, especially the hypervariable exon III 48 bp variable number of tandem repeat (VNTR), have been studied intensively in relation to antipsychotic response to clozapine (53). Although the exon III 48 bp VNTR in *DRD4* does not appear to be a major contributor to clinical outcome during clozapine treatment, it is possible that haplotype analyses incorporating several variants in different locations would be necessary before definitive conclusions can be drawn for the importance of *DRD4* in antipsychotic response. Moreover, studies involving the serotonin receptor gene polymorphisms suggest an association between the 5-HT2A receptor and response to clozapine (53–55). Other neurotransmitters such as norepinephrine, acetylcholine, and glutamate may also contribute to antipsychotic drug effects, but genetic variation in these receptors has not been investigated following a pharmacogenomic perspective (18). A detailed review of polymorphisms in dopamine and serotonin receptor genes, their relevance for response to clozapine and other atypical antipsychotics, and methodologic considerations for application of molecular approaches to psychiatric genetics are available elsewhere (53).

Because the first report more than 60 years ago on the use of amphetamine in children with attention deficit hyperactivity disorder (ADHD), it became clear that approximately 75% of ADHD cases show clinically significant improvement after d-amphetamine or methylphenidate treatment. Although the precise mechanism of action of these stimulant agents still remains elusive, their interaction with the dopamine transporter may contribute to their ther-

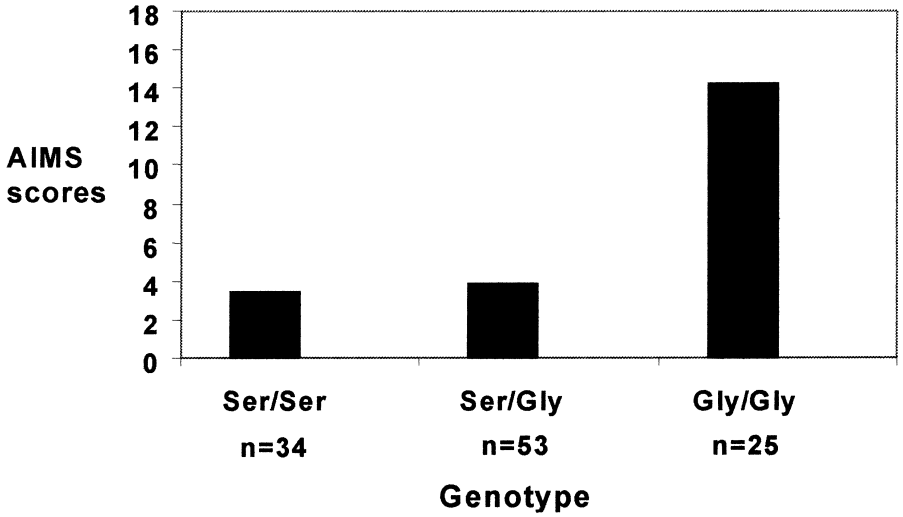

FIGURE 37.3. Average Abnormal Involuntary Movement Scale (AIMS) scores in 112 schizophrenic patients previously treated with typical antipsychotics and genotyped for the serine to glycine polymorphism in the N-terminal extracellular domain of the dopamine D3 (DRD3) receptor. A post hoc Student-Newman-Keuls test revealed a higher average AIMS score in patients homozygous for the glycine allele of the DRD3 gene, compared to those with a heterozygous or homozygous genotype for the serine allele. The analysis of variance results were corrected for age, gender, ethnicity and pairwise comparisons ($F = 8.25$, $df = 2$, $P < 0.0005$ [$P < 0.0015$, Bonferroni corrected]). Reprinted with permission from Basile VS, Masellis M, Badri F, et al. Association of the MscI polymorphism of the dopamine D3 receptor gene with tardive dyskinesia in schizophrenia. *Neuropsychopharmacology* 1999;21:17–27.

apeutic effects in ADHD. The VNTR polymorphism of the dopamine transporter gene appears to influence the response to methylphenidate, based on a preliminary study in 30 African-American children with ADHD (56). These limited data, however, do not allow generalizations on genetic determinants of response to pharmacologic interventions in ADHD at the present time.

The marked temporal delay in therapeutic effects is a well-known phenomenon with antidepressant agents. Therefore, it is advantageous to identify beforehand the subpopulation of patients who are unlikely to respond to a given medication so that various augmentation efforts can be initiated promptly. The high-affinity serotonin transporter (5-HTT) is a prime target for the serotonin reuptake inhibitor antidepressants (SSRIs). A functional polymorphic variant of the *5-HTT* gene characterized by a 44-bp insertion in its promoter region leads to differences in the amount of *5-HTT* transcript and the extent of 5-HT reuptake (57). Clinical studies suggest that the 44-bp insertion polymorphism of the *5-HTT* gene influences the antidepressant response to SSRIs including fluvoxamine and paroxetine (57). Further studies with other SSRIs and classical tricyclic antidepressants are called for to assess the overall clinical significance of *5-HTT* promotor polymorphism(s).

P-glycoprotein encoded by the *MDR1* gene is another drug transporter that affects transmembrane efflux and intracellular or tissue availability of numerous drugs. For example, amitriptyline (but not fluoxetine) can penetrate the brain more readily in knockout mice that do not express p-glycoprotein (58). Hence, differences in *MDR1* expression owing to genetic polymorphisms or secondary to chronic antidepressant treatment may explain treatment-resistance to amitriptyline in patients who otherwise attain therapeutic plasma drug concentrations.

The study of pharmacogenetic polymorphisms in drug targets is a relatively new but rapidly expanding research area. It is likely that molecular genetic profiling of patients for SNPs or other types of human genetic variation in both pharmacokinetic and pharmacodynamic targets will bring psychiatric genetics and clinical pharmacology one step closer to achieve the ultimate goal of individualized therapeutics.

PHARMACOGENOMICS AND DRUG DISCOVERY

The drug discovery in psychiatry was initially based on serendipity. The identification of lithium in 1949 and chlorpromazine in 1950s are two well-known examples where putative mechanisms of action were elucidated after the drugs were shown to be efficacious. The newer drug discovery paradigms have depended on the synthesis and identification of novel compounds through combinatorial chemis-

try and screening for biological activity against known receptors or other biological targets with established endogenous ligands or substrates (59,60). With the Human Genome Project approaching to its completion, essentially all human genes will be available as potential drug targets. The challenge in drug discovery will then be to discern the function and therapeutic utility of these genes and their expressed products.

The experimental paradigms used by pharmacogenomics borrow substantially from the field of population genetics and the methodology used in earlier genetic studies of common complex diseases (60,61). For example, linkage and association studies are two well-known strategies to identify the genes causing a specific disease or variability in drug effects. The linkage design was traditionally used to test the relationship between inheritance of a complex disease phenotype within family members and microsatellite markers comprised of five or less short tandem repeats of DNA. The increasing availability of SNP markers and the ability to genotype the entire genome of large segments of patient populations with ultrahigh throughput methods such as the DNA microarrays, often referred to as "DNA chips," now allow the application of genetic linkage or association designs to elucidate the genes responsible for variations in therapeutic response and toxicity. On the other hand, the obvious difficulties in administering drugs to different family members and obtaining relevant data on drug response phenotype may pose a constraint on application of linkage design to pharmacogenomics.

DNA microarray is an emerging powerful technological breakthrough that enables the study of global gene expression patterns and sequence variations at a genome level (62). In essence, DNA microarray is an extension of the Southern blot procedure and is comprised of different cDNAs or oligonucleotides etched systematically on a solid surface such as silica or glass plate. Each DNA species on the array represents a specific gene or expressed sequence tag, which is used to identify different SNPs or transcripts by hybridization and fluorescence detection. Microarrays with 10,000 or more genes are now available for use in clinical research or trials. An important application of microarrays is monitoring of temporal changes in gene expression during drug treatment or patients versus healthy individuals. The premise in these studies is that patterns of gene expression may serve as indirect clues about disease-causing genes or drug targets. Moreover, the effects of drugs with established efficacy on global gene expression patterns may provide a guidepost, or a "genetic signature," against which the new drug candidates can be validated (63). Other new genomic technologies such as genotyping by mass spectrometry also are being developed. Collectively, pharmacogenomics adds another dimension to contemporary drug discovery efforts because it aims to identify novel drug targets in the *entire* human genome without *a priori* assumptions on disease pathogenesis or drug targets, thereby presenting an opportunity to unlock unprecedented novel mechanisms of drug action (4).

PHARMACOGENOMICS AND DRUG DEVELOPMENT

After the discovery of an NCE with therapeutic potential, the next step involves clinical testing in healthy volunteers and relevant target patient populations. For every clinician, an appreciation of the drug development process is important to make evidence-based choices among therapeutic alternatives and to be aware of the shortcomings of the data presented to support the efficacy and safety of new medications.

The drug discovery and development is a high-risk venture. Typically, it takes 8 to 12 years to introduce a new drug from discovery to clinical practice, with costs often approaching $100 to $300 million. On the other hand, it is estimated that approximately 90% or more of NCEs under development fail to meet the regulatory approval for clinical use (64). It is well known to most pharmaceutical scientists that the art of timely and cost-effective drug development rests on early identification and removal of drug candidates with poor efficacy and safety. It is conceivable that some of these NCEs may in fact have a favorable efficacy and safety profile in certain genetically determined subpopulations. Through proper design of clinical trials and using low-cost high-throughput genetic analyses, pharmacogenomics eventually can allow patenting of such "failed" NCEs in discrete patient populations and reinstate their market potential. In addition, a genetic test predicting drug effects would be considered another pharmaceutical product and an additional financial incentive for drug developers. For example, clozapine was recognized as a potential antipsychotic drug in early 1970s. The occurrence of agranulocytosis in several cases caused the termination of further development of clozapine in treatment-resistant patient populations until the late 1980s. The presence of genetic or other predictors of agranulocytosis would have expedited the development of clozapine and prevented the inconvenience of periodical hematologic monitoring.

Pharmacogenomics is also relevant for better use of medications that are already in routine clinical use (phase 4 drug development). A recent meta-analysis of prospective studies from 1966 to 1996 found that the incidence of serious and fatal adverse drug reactions in United States was 6.7% and 0.32%, respectively; ranking between the fourth to sixth leading cause of death, ahead of pneumonia and diabetes (65). Importantly, the adverse drug reactions in the latter study occurred during treatment with usual doses of drugs that already met the regulatory requirements for clinical use, and excluded cases owing to intentional or accidental overdose, errors in drug administration, or noncompliance.

It is likely that the proportion of such patients who are inadequately treated may further increase after accounting for therapeutic failures secondary to ultrarapid drug metabolism, for instance, and mismatches between the pharmacodynamic attributes of medications and drug targets in individual patients (23,37). Evidently, the existing pharmacotherapy system based on the traditional trial-and-error approach is unable to deliver personalized drug treatment and health care.

From the perspective of patients, healthcare providers, and managed care organizations, an increased probability of therapeutic response through genetic testing would reduce duration of inpatient hospital care, frequency and inconvenience of repeated physician visits owing to treatment resistance, and thus, easily offset the costs of pharmacogenomic-based drug development. For NCEs that readily meet the regulatory requirements with large efficacy margins (i.e., "blockbuster drugs") over placebo or the existing standard treatment modalities, there may be less financial incentive—on the manufacturers' part—to identify different subpopulations with differing drug effects, because this may potentially decrease the market share of their newly introduced medication. Therefore, although pharmacogenomics provides a clear rationale for improved drug discovery and personalized therapeutics, it will likely need enforcement by regulatory agencies before it can be utilized in routine clinical practice and pharmaceutical industry. This may in turn require amendments to existing regulatory policies for drug development. Also, as a result of the global harmonization attempts to standardize drug development and approval process, the settings of future clinical trials will not only be limited to Western society; therefore, it would be critical and advantageous to plan such policy amendments at a multinational level.

ETHICAL AND HEALTH POLICY CONSIDERATIONS

Pharmacogenomics arrived at the heels of the molecular biology revolution in 1980s and early 1990s. Although there is much optimism for a more efficient drug discovery and development process, there is also increasing concern about the implementation of genetic testing at various levels of the medical practice and its repercussions for health policy and managed care organizations. Confidentiality of the genetic test results is critical because it has important bearings on finding employment and obtaining life, health, or disability insurance. There is an urgent need to amend the existing medical curriculum to educate future clinical personnel for genetic counseling and fundamentals of molecular medicine. About 5% of the budget for the Human Genome Project is reserved to address these social and ethical issues.

CONCLUSION

Personalized therapeutics has been a preoccupation in clinical psychiatry for many decades. The traditional gene-by-gene approach to explain variability in drug response has been a mainstay in most pharmacogenetic investigations to date. However, the biological underpinnings of drug response are complex and often involve contributions by multiple genes, environmental factors, drug–drug and drug–food interactions, to mention a few (Fig. 37.4) (18, 66–71). Clearly, a genome-wide approach will be an important advance in understanding the variability in drug efficacy and safety. To this end, sequence variations in the genome are only the first level of complexity. More intriguing and challenging is establishing the significance of differences in global gene expression patterns in relation to drug effects and targets. High throughput and genome-wide transcript profiling for differentially regulated mRNA species in disease, normal physiology, and after drug treatment offer an additional dynamic perspective for drug discovery. The development of protein chips may permit further explorations of functional genomics in the context of psychopharmacology. We may soon be surprised that the mechanism of action of some psychotropics may in fact rest on targets entirely different than what the conventional pharmacologic wisdom suggests (e.g., the monoamine hypothesis for antidepressant drug effects).

At the present time, however, it is not clear whether and to what extent the genomic hypotheses can be tested within the framework of the available clinical trial methodology. For example, the sample size in most phase 3 clinical trials does not usually exceed 3,000 to 4,000 patients. Genome-wide association studies and statistical correction for multiple testing will require sample sizes well beyond the current resources of any single pharmaceutical company or an academic laboratory. Ideally, pharmacogenomics should be used for the prospective design of phase 3 clinical trials and not to salvage an NCE that proved to be ineffective or unsafe at the end of phase 3 investigations. Care should be taken for adequate representation of each subpopulation identified by genetic markers. The information obtained by genomic methods should ultimately be translated into discrete product labeling information. Otherwise, it is uncertain whether the off-label data available in the form of scientific publications will transform routine clinical practice and lead to personalized therapeutics. Also, genomic data are fundamentally different than the traditional covariates (e.g., weight, age) that have been used to explain variability in drug efficacy and safety, and thus require special considerations. Clear regulatory guidelines and new collaborations between academic institutions and the pharmaceutical industry, both at the level of basic and clinical research, are called for to implement pharmacogenomics in the drug development process and evaluate its significance for achieving drug safety, efficacy and effectiveness (72–74).

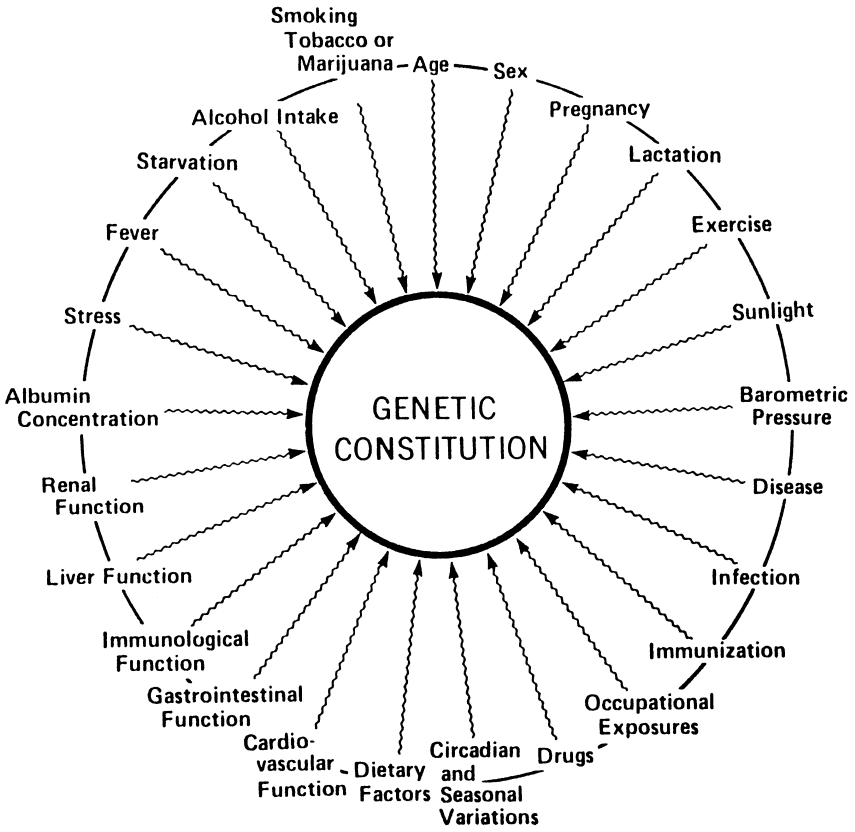

FIGURE 37.4. The interaction of genetic and environmental factors that may influence drug response in humans. Reprinted with permission from Vesell ES. On the significance of host factors that affect drug disposition. *Clin Pharmacol Ther* 1982;31:1–7.

Pharmacogenomics emerged in late 1990s by coalescence of traditional methodologies used in human genetics, common complex diseases and pharmacogenetics, together with the impetus provided by novel genomic technologies developed as part of the Human Genome Project. The collection of genomic data is being more feasible by increasing accessibility and decreasing costs of molecular genetic analyses. Pharmacogenomics has far-reaching implications in medicine and biology and can be applied to various facets of therapeutics from drug discovery and neuroimaging to drug–drug and drug–food interactions (5,6,75). The road from pharmacogenomics to personalized therapeutics is arduous and challenging but the technology is now in place to validate the utility of pharmacogenomics in routine clinical practice and pharmacotherapy (76).

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