Advances in Pharmacogenetics and Pharmacogenomics

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Large differences among normal human subjects in the efficacy and safety of many therapeutic agents are caused by genetically controlled polymorphisms of drug-metabolizing enzymes, drug transporters, and drug receptors. Development of pharmacogenomics as a new field has accelerated progress in pharmacogenetics by elucidating at the level of the human genome the inherited basis for those large interindividual variations. Examples discussed in this review illustrate how this approach can be used not only to guide new drug discovery but also to individualize therapy. Adverse drug reactions, often attributable to large differences among subjects in drug response, constitute a leading cause of death in the USA. Such high morbidity and mortality could be reduced by application of the principles of pharmacogenetics and pharmacogenomics, defined broadly as the study of genetically caused variability in drug response.

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DEFINITIONS

Pharmacogenetics is usually defined as the study of hereditary variations that underlie differences among humans in drug response. Traditionally, these genetically controlled variations have been subdivided into those affecting pharmacokinetic processes and those affecting pharmacodynamic processes. Pharmacogenomics represents a natural development or evolution of successful pharmacogenetic research by applying genomic techniques to hasten identification of new drug response markers, whether those markers act at the level of drug metabolism, drug target, or disease pathway.[1-3] The underlying principle of pharmacogenomics is that for many commonly occurring diseases, such as cancer, atherosclerosis, and the neurodegenerative disorders, each comprises a group of genetically discrete entities with a similar clinical end point or phenotype but separate molecular etiologies and therefore possibly different responses to therapy.

HISTORICAL PERSPECTIVE

Even before the term *pharmacogenetics* was coined, physicians had long recognized the occurrence of familial clustering of unusual responses to drugs and suspected a biochemical genetic basis for these drug toxicities. The developments that led to the creation of this subject as a new field took place in the mid-1950s and also in the 1960s. Even before then, the first pharmacogenetic conditions, inability to taste phenylthourea and acatalasia, were described in 1932[4] and 1952,[5] respectively. In 1957, Motulsky[6] published a seminal article in which approximately a dozen diverse genetic conditions were considered together because each was associated with a toxic reaction to a specific drug or environmental chemical. Furthermore, each condition arose from a mutation in an enzyme involved in the metabolism of a particular drug, thereby causing toxic accumulation of that drug due to blockage of its usual pathway of degradation.

Motulsky foresaw that detection of these genetically transmitted traits, unified by their capacity to produce adverse drug responses, could be significant in human genetics by virtue of their potential relationship to human susceptibility or resistance to other diseases. He also realized that they served as models for the interaction of heredity and environment in the pathogenesis of disease.

In 1959, Vogel coined the term *pharmacogenetics*,[7] and in 1962, Kalow wrote the first comprehensive textbook on pharmacogenetics.[8] In 1968, Vesell and Page[9-11] showed that large interindividual variations, ranging from 4- to 40-fold depending on the drug and the population studied, vanished within sets of healthy human

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monozygotic twins but were preserved within many, though not all, dizygotic twinships. These results indicated that in humans, under the conditions of the experiments, for the numerous drugs studied, large interindividual variations in rates of metabolic elimination were under predominantly genetic rather than environmental control. When genetic variations disappeared, as in monozygotic twins, so too did the pharmacokinetic variations in rates of drug elimination. These twin studies also implicated a relatively small number of genetic loci involved in controlling interindividual variations in drug clearance since about a third of the dizygotic twinships investigated were as similar in their pharmacokinetic values as the monozygotic twinships (Figure 1). These conclusions on the genetic control of large interindividual variations in rates of eliminating specific drugs were extended to the phenomenon of induction. After chronic administration of an inducing drug such as phenobarbital, large interindividual variations occurred among dizygotic but not monozygotic twins in the extent to which their elimination rates were accelerated (induction).[12]

While the twin studies established the important role of genetic factors in controlling large interindividual variations in rates of human drug elimination measured in vivo, they did not reveal the specific enzymes or genes that were involved. That advance had to await the 1980s and the isolation and characterization of the individual hepatic cytochrome P450s (CYPs) of which there are now recorded approximately 49 genetically distinct human forms.

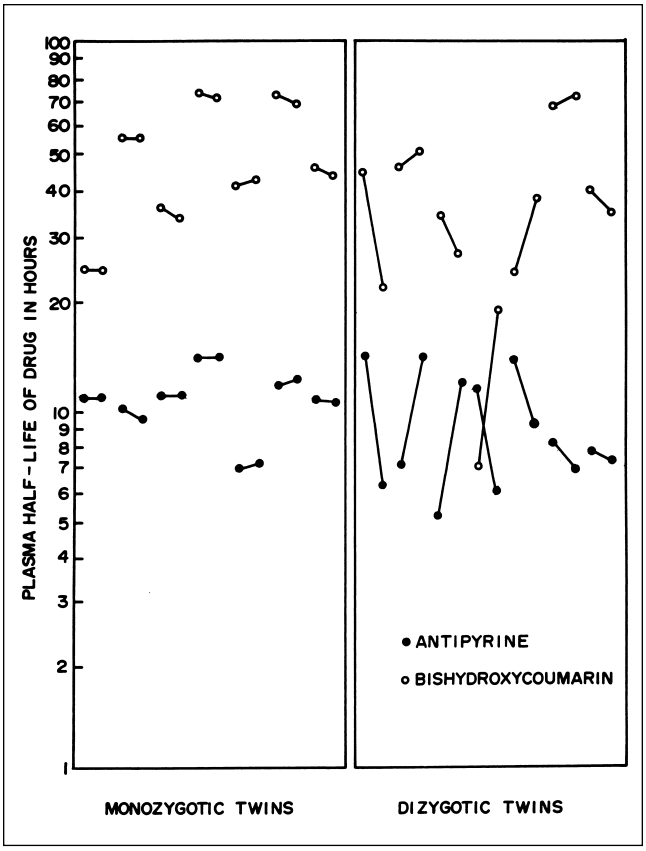

Figure 1. Plasma half-lives of bishydroxycoumarin (open circles)[11] and antipyrine (filled circles)[10] were measured in monozygotic and dizygotic twins after a single dose of each drug. An interval of 6 months separated administration of bishydroxycoumarin and antipyrine. A solid line joins values within each twinship.

CYP POLYMORPHISMS

It is now recognized that while genetic polymorphisms occur in most, if not all, human cytochrome P450 (CYP) isozymes, most functional genetic polymorphisms reside in only four: CYP2A6, CYP2C9, CYP2C19, and CYP2D6.[3,13] These four functionally polymorphic CYPs account for approximately 40% of all drug metabolism mediated by CYP isozymes.[3,13] Fresh mutations at these four genetic loci are being discovered and new alleles described so rapidly, that a Web site has been established to track them (http://www.imm.ki.se/cypalleles/) (Table I).[3,13] In addition, CYP3A4, which is responsible for approximately 50% of all CYP-mediated drug metabolism,[13] has recently been demonstrated to exhibit functional mutations that attain in different ethnic groups the frequency required for a genetic polymorphism (1% or more).[14] CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12 have been identified and evidence presented for an allelic variant with markedly altered catalytic activity for the substrate nifedipine.[14] Thus, rather than being exceptional in human drug metabolism, genetically controlled variations are common and are recognized as having profound pharmacological consequences. Drugs are almost all metabolized by phase I and/or phase II enzymes. Phase I enzymes act, often through CYPs, to oxidize a drug, rendering it more susceptible to conjugation reactions performed by phase II enzymes. It is anticipated that these drug-metabolizing enzymes will be found to be controlled by hundreds of genes once the human genome is deciphered. For example, for only the CYP2D6 shown in Table I, 48 distinct mutations and 53 alleles have been identified in a European population.[15] Examples of representative pharmacogenetic conditions exclusive of most CYP polymorphisms are listed in Table II.

At the present time, many mutations of pharmacogenetic interest have been elucidated at the genomic

Table I Human Polymorphic Cytochrome P450 Enzymes and Ethnic Differences in Distribution of Their Major Variant Alleles

Enzyme	Major Variant Alleles	Mutation	Consequences for Enzyme Function	Allele Frequencies (%)			
				Caucasians	Asians	Black Africans	Ethiopians and Saudi Arabians
CYP2A6	*CYP2A6*2*	Leu160His	Inactive enzyme	1-3	0	ND	ND
	CYP2A6del	Gene deletion	No enzyme	1	15	ND	ND
CYP2C9	*CYP2C9*2*	Arg144Cys	Reduced affinity for P450 oxidoreductase	8-13	0	ND	ND
	*CYP2C9*3*	ll359Leu	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*	Thr107lle, Arg296Cys, Ser486Thr	Reduced affinity for substrates	0	ND	34	3-9

Reproduced from Ingelman-Sundberg et al.[13]
ND, no data.

level, permitting more precise definition of a specific clinical syndrome associated with each mutation than previously possible, a field designated functional genomics. Before the ready accessibility of these techniques, several discrete clinical syndromes were unavoidably combined since, on occasion, genetically distinct mutations affecting a single drug-metabolizing enzyme could not be distinguished from one another. Now that the whole human genome is about to be unraveled and fully deciphered (see the concluding Future Developments section of this review), we are entering a new era of research in pharmacogenetics and pharmacogenomics that offers many exciting, innovative opportunities.

PHARMACOGENETICS AND DRUG RESPONSE MARKERS

This broadening scope of pharmacogenetics and its development into pharmacogenomics have appealed to the pharmaceutical industry as potentially rich sources of new drugs that target specific lesions, allowing for individualized therapy. Clearly, genetic differences among patients can either themselves constitute or else be closely associated on the chromosome with drug-response markers at the level of drug metabolism, drug target, or disease pathway. These developments at the level of drug target or disease pathway are relatively recent offshoots of pharmacogenetic research; accordingly, few data are available. In several instances, these data are incomplete, complex, or even conflicting. However, the future promise of this research is so great that a brief review of some innovative, if preliminary, contributions and ideas will be undertaken.

DRUG-RESPONSE MARKERS AT THE LEVEL OF DRUG TARGET

In an earlier review of genetic variation as a guide to drug development, we cited several examples at the level of drug target.[1] One of these was a report of a structural polymorphism in the serotonin 5-HT_{2A} receptor associated with the clinical response of schizophrenic patients to the atypical antipsychotic clozapine.[16] This polymorphism consists of a tyrosine substitution for histidine at the 452 position of the 5-HT_{2A} receptor. The His452Tyr allele occurred twice as frequently in schizophrenic patients resistant to clozapine as in those re-

Table II Partial List of Pharmacogenetic Conditions

Reduced enzyme activity or defective protein
- N-acetylation polymorphisms (*NAT2*, *NAT1*)
- Drug-induced hemolytic anemia (G6PD deficiency)
- Hereditary methemoglobinemias; hemoglobinopathies
- Null mutants of glutathione transferase, mu class (*GSTM1*); theta class (*GSTT1*)
- Thiopurine methyltransferase deficiency (*TPMT*)
- Paraoxonase deficiency
- UDP glucuronosyltransferase (Gilbert's disease, *UGT1A1*; (*S*)-oxazepam, *UGT2B7*)
- NAD(P)H:quinone oxidoreductase (*NQO1*)
- Epoxide hydrolase (*HYL1*)
- Atypical alcohol dehydrogenase (ADH)
- Atypical or absent aldehyde dehydrogenase (*ALDH2*)
- Defect in converting aldophosphamide to carboxyphosphamide (*ALDH1A1?*)
- Alpha-one (α_1)-antitrypsin (*PI*)
- Alpha-one (α_1)-antichymotrypsin (*ACT*)
- Angiotensin-converting enzyme (*DCP1*, *ACE*)
- Acatalasemia (*CAT*)
- Dihydropyrimidine dehydrogenase (*DPD*)
- Succinylcholine sensitivity, atypical serum cholinesterase (*CHE1*)
- Cholesteryl ester transfer protein (*CETP*)
- Butyrylcholinesterase (*BCE1*)
- Fish odor syndrome (*FMO3*)
- Glucocorticoid-remediable aldosteronism (*CYP11B1*, *CYP11B2*)
- Dubin-Johnson syndrome; multispecific organic anion transporter (*MOAT*, *MRP*)
- Altered serotonin transporter (*5HHT*)
- Altered dopamine transporter (*DAT*)
- Dopamine receptors (*D2DR*, *D4DR*)
- Defective drug transporters (e.g., MDR1), resistance to chemotherapeutic agents
- Licorice-induced pseudoaldosteronsim (*HSD11B1*)
- Mineralocorticoid excess with hypertension (*HSD11B2*)
- Pyridoxine (vitamin B6)-responsive anemia (*ALAS2*)

Increased resistance to drugs or chemicals
- Inability to taste phenylthiourea (PTU)
- Coumarin anticoagulant resistance (receptor defect)
- Androgen resistance

Increased resistance to drugs or chemicals
- Estrogen resistance
- Cushing's syndrome from low doses of dexamethasone
- Insulin resistance
- Rhodopsin variants; dominant form of retinitis pigmentosa
- Vasopressin resistance (*AVPR2*)
- Increased metabolism—atypical liver alcohol dehydrogenase (*ADH*)
- Defeceive receptor—malignant hyperthermia/general anesthesia (Ca^{++} release channels ryanodine receptor) (*RYR1*, *MHS1*)

Change in response due to enzyme induction
- Porphyrias (esp. cutanea tarda)
- Aryl hydrocarbon receptor (AHR) polymorphism (CYP1A1, CYP1A2 inducibility polymorphism)

Abnormal metal distribution
- Iron (hemochromatosis, *HFE*)
- Copper (Wilson's disease, Menkes's disease)

Familial disorders of unknown etiology
- Corticosteroid (eye drops)–induced glaucoma
- Halothane-induced hepatitis
- Chloramphenicol-induced aplastic anemia
- Aminoglycoside antibiotic-induced deafness
- Beryllium-induced lung disease
- Hepatitis B vaccine resistance
- Long-QT syndrome
- Retinoic acid resistance and acute promyelocytic leukemia
- Thombophillia (activated protein C resistance)
- Lactose intolerance
- Fructose intolerance
- Beeturia (red urine after eating beets)
- Malodorous urine after eating asparagus
- Reproductive disadvantage in ΔF508 cystic fibrosis heterozygotes who smoke cigarettes (*CFTR*)
- High risk of cerebral vein thrombosis in defective prothrombin (*F2*) heterozygotes
- High risk of cerebral vein thrombosis in users of oral contraceptives

Adapted from Nebert.[3]

sponding to it. This observation, which requires confirmation, suggests that the mutant allele somehow changes the structure of the serotonin ($5\text{-}HT_{2A}$) receptor, thereby altering the binding properties of the drug at this site and reducing clozapine's efficacy. However, the topic of association between genetic polymorphisms in genes for serotonin receptors and risk of developing schizophrenia, as well as response of schizophrenic patients to clozapine therapy, is highly controversial. For example, Lin et al[17] observed in a Taiwanese population no association between another genetic polymorphism of a $5HT_{2A}$ receptor (102T/C)

and either schizophrenia or response to clozapine. By contrast, Inayama et al,[18] Williams et al,[19] and Erdmann et al[20] reported a positive association between the $5HT_{2A}$ polymorphism 102T/C and schizophrenia. Nevertheless, the negative results of Lin et al[17] in a Taiwanese population agree with those of three other studies[21-23] that claimed no association between the 102T/C polymorphism and schizophrenia.

Lin et al offered several explanations for these discrepant results.[17] First, chance alone could have caused the positive associations. Second, the observed odds ratios were small, suggesting that the genetic polymorphism contributes only a small portion to the total risk of developing schizophrenia. Third, failure to observe a positive association between the 102T/C polymorphism and schizophrenia may be a false-negative result arising from small sample size and a consequent low statistical power. Fourth, the gene effect of this polymorphism may be significant but so small that in some studies, it has eluded detection. Fifth, the case control method used in these studies is exceedingly sensitive to subtle differences in the sample selected, including differences of age, gender, or geography. Thus, for example, the allele frequencies of the 102T/C polymorphism differ according to ethnic origin of the population selected for study; allele frequencies of 102T were higher in Chinese and Japanese populations[18,22] than in Western studies,[19-21,23] where the 102C allele was higher. Finally, a stratification effect may be operative, resulting from a different severity of schizophrenia in the patients or controls selected for study. Using several methods, Verga et al[24] investigated the 102T/C polymorphism in schizophrenic patients and observed no difference in genotypes between patients or controls. In 1999, Younger et al[25] reported in a Taiwanese population an association between a genetic polymorphism (C267T) and schizophrenia in a different serotonin receptor, the serotonin-6 receptor (5HT6).

A preliminary report claimed an association in a group of Taiwanese schizophrenic patients between a polymorphism in still another receptor, the dopamine D_2 receptor, and susceptibility to tardive dyskinesia (TD) after long-term treatment with neuroleptics.[26] In these 93 patients, when considered together, results were only marginally significant, but when subgrouped according to sex, female schizophrenic patients with the A2 allele at this locus were clearly more susceptible to TD than non-TD female patients. Other pharmacogenomic examples at the level of drug target include overexpression of thymidylate kinase[27] and dihydrofolate reductase,[28] mechanisms by which tumor cells acquire resistance to the antimetabolites 5-fluorouracil and methotrexate, respectively. In this case, cellular levels of target enzyme can exceed the highest amount of drug safely attainable in the patient. Several therapeutic approaches to enhance the antitumor efficacy of these antimetabolites focus on inhibition of the overexpressed enzymes and their genes.

Another example of the search for drug response markers at the level of drug target is that of p53, the tumor suppressor protein sometimes called the "guardian of the genome." This protein responds to mutations in DNA by stopping cell division or causing apoptosis, thereby preventing tumor spread. However, since mutations in p53 often precede tumor formation, one recent approach to restore function of mutant p53 as a DNA guardian is to provide a molecular brace, thereby regenerating the capacity of mutant p53 to bind avidly once again to DNA.[29] More than 100,000 compounds were screened to determine if any might bind to mutant p53 in cultured tumor cells to restore its altered structure. One such compound was identified, but it required very high doses. Compounds of greater potency will have to be developed before their potential as anticancer drugs can be tested, but the approach seems promising.

Another quite different approach to cancer therapy also uses p53 and chemicals that bind it.[30] In this case, the molecule, pifithrin-α, was designed to inhibit p53, not to restore its function, in normal tissues of animals with tumors. The concept is to protect normal tissues of animals receiving antitumor therapy such as gamma radiation from the apoptosis normally produced by p53 in damaged cells. Several important normal tissues that contain high concentrations of p53, such as bone marrow stem cells, are damaged by anticancer therapy. The extent of this damage correlates directly with p53 activity. Accordingly, a p53 inhibitor, pifithrin-α, was developed to protect normal mouse tissues from the lethal genotoxic side effects of anticancer therapy without promoting tumor formation. Initial results in mice are promising.

DRUG-RESPONSE MARKERS AT THE LEVEL OF DISEASE PATHWAY

The recognition that certain genetic variations are associated with altered risk of acquiring some diseases as well as with altered drug response offers powerful new opportunities not only to identify earlier individuals who will develop these diseases but also to improve their therapy by increasing efficacy and specificity of treatment. Pharmacogenomics provides such potential, and the following are presented as initial examples. Several of these examples require confirmation and/or extension.

The first example again involves p53. Here human colon cell lines, after their p53 was specifically disrupted by targeted homologous recombination, exhibited profound alterations in their drug responses.[31] For drugs that act as DNA-damaging agents, such as doxorubicin, there was observed enhanced cell-destructive capability, whereas for drugs that act post-transcriptionally, such as 5-florouracil (5-FU), a mainstay of antitumor therapy in colon cancer, there occurred profound resistance. Thus, the status of p53 in colon cancer cells is apparently a critical factor in their response to certain drugs. Mutations of p53 in these cells would suggest that DNA-damaging drugs such as doxorubicin be selected as antitumor agents, rather than drugs such as 5-FU that act posttranscriptionally by perturbing RNA.[31]

The second example involves infectious diseases and the association of specific genetic loci with altered susceptibility to infections and possibly also response to drug therapy. In inbred mouse strains, a single dominant gene (Bcg) controls susceptibility to various infections, including tuberculosis, leprosy, leishmaniasis, and salmonellosis. The phenotype designated Bcgs is associated with increased sensitivity; that designated Bcgr is associated with increased resistance. In these mouse strains, positional cloning disclosed a candidate gene, called the natural resistance-associated macrophage protein 1 gene (Nramp 1), expressed exclusively in reticuloendothelial cells. The polymorphism in this gene arises from substitution of a single amino acid, aspartic, for glycine at position 169. A human homologue of the mouse Nramp 1 gene has been identified and designated *NRAMP1*.[32,33] Moreover, genetic variation in *NRAMP1* affects susceptibility to tuberculosis in West Africans in a manner generally analogous to that described in the mouse studies.[32,33] However, susceptibility to these infections depends as well on additional ethnic factors and varies accordingly.[34,35]

The third example consists of a genetic polymorphism defined by an insertion (I) or deletion (D) of a 287-bp DNA fragment, suspected to be a silencer element, in the gene that transcribes the angiotensin- converting enzyme (ACE) and controls its function. Approximately 47% of all variance in serum ACE activity is controlled by this genetic polymorphism.[36,37] Moreover, this polymorphism has been associated with altered responsiveness to treatment with ACE inhibitors of certain renal diseases[38-40] as well as hypertension[41] and heart failure.[42]

The fourth example is the well-established association between the allele for apolipoprotein E type 4 (APOE-E4) and the common late-onset familial as well as sporadic forms of Alzheimer's disease (AD).[43] The latter forms have been localized on human chromosome 19 very close to the APOE locus. Not only is increasing dose of the APOE-E4 allele associated with increasing risk of development of AD but also with an earlier age of disease onset. Moreover, there is an association of the APOE-E4 allele with a markedly decreased response to treatment with the cholinesterase inhibitor tacrine.[44]

The fifth example involves a genetic polymorphism of the cholesteryl ester transfer protein (CETP). The presence or absence of a restriction site for the enzyme TaqI in intron I of CETP is designated B1 or B2, respectively. In a controlled, randomized trial of 807 Dutch men with angiographically documented coronary atherosclerosis, the control group that received placebo for 2 years showed most atherosclerotic progression in subjects with the B1 genotype and least in those with the B2 genotype. In the treatment group—those receiving the cholesterol-lowering drug pravastatin—only patients of the B1 genotype decreased progression of their coronary atherosclerosis compared to those of the B1 genotype in the control group.[45] Once again, therapeutic benefit seems selective for a specific genotype (B1); therapeutic resistance occurs for a different genotype (B2). An explanation for this difference in outcome involves the metabolic function of CETP. Higher serum levels of CETP are normally associated with lower serum concentrations of high-density lipoprotein (HDL), a situation tending to encourage development of atherosclerosis. In these 807 Dutch subjects with coronary atherosclerosis, the B1 variant of CEPT conferred increased serum CEPT and decreased HDL concentrations. Thus, effects of the CEPT genetic polymorphism on progression of atherosclerosis can be interpreted according to the influence of each genotype on CEPT concentration and consequent HDL levels.

The sixth example is the congenital long-QT syndrome, caused by mutations in cardiac potassium-channel genes *KVLQT1* at the LQT1 locus, *HERG* at the LQT2 locus, and the sodium-channel gene *SCN5A* at the LQT3 locus.[46] The long-QT syndrome predisposes to *torsades de pointes* and ventricular fibrillation. The genotype of subjects with the long-QT syndrome influences its clinical course; risk of cardiac arrhythmias becomes significantly higher in subjects having mutations at the LQT1 and LQT2 loci than among those with mutations at the LQT3 locus. Cumulative mortality is similar regardless of genotype, but the percentage of lethal cardiac events is higher in families having LQT3 mutations.[46] In addition, cloning and characterization of a gene for another potassium channel peptide, mink-related peptide 1 (*MiRP1*), have been described and three missense mutations of this gene identified; these

mutations are associated with long-QT syndrome and ventricular fibrillation.[47] Peptides from these mutant genes form channels that open slowly and close rapidly, thus retarding potassium currents. Of interest to pharmacogenetics and pharmacogenomics, one variant is associated with clarithromycin-induced arrhythmia by causing this antibiotic to blockade the channel.[47]

The seventh example revisits cancer, the first disease discussed. A possible association was investigated between the benefit of adjuvant therapy for early-stage breast cancer and a marker gene, the gene that controls c-*erb*B-2 (also known as *HER2/neu*) expression. In both this initial study of 397 patients,[48] as well as a later expanded study that included 595 additional patients,[49] women with breast cancer at this relatively early stage (< 9 positive axillary nodes) who overexpressed c-*erb*B-2 had a dose-dependent response to adjuvant therapy, with best results at highest doses. Women with low expression of c-*erb*B-2 showed no such dose-response relationship. However, in another much smaller study by a different group of investigators, 25 women with breast cancer who received adjuvant therapy at a later stage of the disease (> 9 positive axillary nodes) exhibited no association between the extent of c-*erb*B-2 expression and drug response.[50] The adjuvant therapy consisted of cycles of a combination of cyclophosphamide, doxorubicin, and 5-fluorouracil. This example illustrates the crucial role played by various host factors, as well as patient selection, patient number, stage of disease, and study design, in evaluating the response of patients with breast cancer to adjuvant therapy.

FUTURE DEVELOPMENTS

Despite the preliminary nature of several of these observations, which are based primarily on epidemiological evidence rather than the more dependable prospective, randomized controlled clinical trial, these results collectively suggest a bright future for pharmacogenomic research and for the opportunities it offers to improve therapy through the use of genetic variation as a guide to individualize drug administration. Furthermore, recent progress in decoding the human genome augers well for the future of pharmacogenomics. For example, the Celera Corporation of Rockville, Maryland announced that it had analyzed some 10 million human DNA fragments that include 5.3 billion bases.[51] (The entire human genome, containing approximately 3 billion bases, needs to be sequenced six times over to achieve a fully accurate assembly.) Thus, the complete human genome should soon become available to identify drug response markers at the levels of drug metabolism, drug target, or disease pathway. When the whole human genome is deciphered, it should be possible to accelerate progress in pharmacogenomic research by including the methods of linkage and association analysis in families, previously used so successfully in investigating disease-causing mutations in humans but thus far, due to technical problems discussed elsewhere,[1] inaccessible in pharmacogenomic research.

As illustrated by most of the pharmacogenomic examples cited in this review, advances previously have depended mainly on identification in the genome of single-nucleotide polymorphisms (SNPs). These arise from mutations affecting a single nucleotide, occur relatively frequently (approximately once in every 500 base pairs), and must exceed in a population a frequency of 1% to meet the requirement of a genetic polymorphism. Exceedingly active research in this field has led to the discovery of a few thousand SNPs in or near functional genes of interest, as well as in seemingly nonfunctional, nontranslatable DNA; many thousand more SNPs remain to be localized and described. Recent technical advances will accelerate such progress by permitting more rapid elucidation and assessment of nucleotide sequences; these include DNA array technology, high-throughput screening systems, and advanced bioinformatics. Collectively, all these developments should make the future of pharmacogenomics very bright.

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