# Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics

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# Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics

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**Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to interindividual differences in the efficacy and toxicity of many medications. Pharmacogenomic studies are rapidly elucidating the inherited nature of these differences in drug disposition and effects, thereby enhancing drug discovery and providing a stronger scientific basis for optimizing drug therapy on the basis of each patient's genetic constitution.**

There is great heterogeneity in the way individuals respond to medications, in terms of both host toxicity and treatment efficacy. Potential causes for such variability in drug effects include the pathogenesis and severity of the disease being treated; drug interactions; and the individual's age, nutritional status, renal and liver function, and concomitant illnesses. Despite the potential importance of these clinical variables in determining drug effects, it is now recognized that inherited differences in the metabolism and disposition of drugs, and genetic polymorphisms in the targets of drug therapy (such as receptors), can have an even greater influence on the efficacy and toxicity of medications. Clinical observations of such inherited differences in drug effects were first documented in the 1950s, exemplified by the relation between prolonged muscle relaxation after suxamethonium and an inherited deficiency of plasma cholinesterase (*1*), hemolysis after antimalarial therapy and the inherited level of erythrocyte glucose 6-phosphate dehydrogenase activity (*2*), and peripheral neuropathy of isoniazid and inherited differences in acetylation of this medication (*3*). Such observations gave rise to the field of "pharmacogenetics," which focuses largely on genetic polymorphisms in drug-metabolizing enzymes and how this translates into inherited differences in drug effects [reviewed in (*4*)].

The molecular genetic basis for these inherited traits began to be elucidated in the late 1980s, with the initial cloning and characterization of a polymorphic human gene encoding the drug-metabolizing enzyme debrisoquin hydroxylase (*CYP2D6*) (*5*). Genes are considered functionally "polymorphic" when allelic variants exist stably in the population, one or more of which alters the activity of the encoded protein in relation to the wild-type sequence. In many cases, the genetic polymorphism is associated with reduced activity of the encoded protein, but there are also examples where the allelic variant encodes proteins with enhanced activity. Since the cloning and characterization of *CYP2D6*, human genes involved in many such pharmacogenetic traits have been isolated, their molecular mechanisms have been elucidated, and their clinical importance has been more clearly defined. Inherited differences in drug-metabolizing capacity are generally monogenic traits, and their influence on the pharmacokinetics and pharmacologic effects of medications is determined by their importance for the activation or inactivation of drug substrates. The effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) (*6*) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codeine) (*7*).

However, the overall pharmacologic effects of medications are typically not monogenic traits; rather, they are determined by the interplay of several genes encoding proteins involved in multiple pathways of drug metabolism, disposition, and effects. The potential polygenic nature of drug response is illustrated in Fig. 1, which depicts the hypothetical effects of two polymorphic genes: one that determines the extent of drug inactivation and

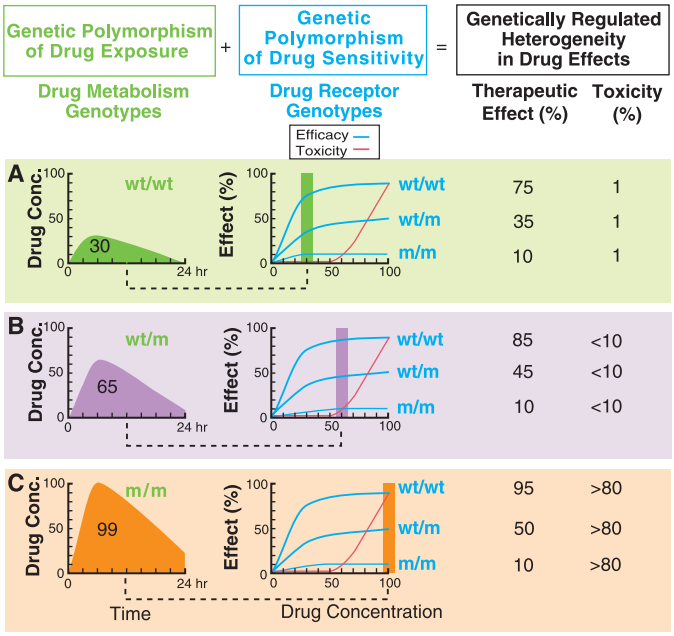


**Fig. 1.** Polygenic determinants of drug effects. The potential consequences of administering the same dose of a medication to individuals with different drug-metabolism genotypes and different drug-receptor genotypes is illustrated. Active drug concentrations in systemic circulation are determined by the individual's drug-metabolism genotype (green lettering), with (**A**) homozygous wild type (wt/wt) patients converting 70% of a dose to the inactive metabolite, leaving 30% to exert an effect on the target receptor. (**B**) For the patient with heterozygous (wt/m) drug-metabolism genotype, 35% is inactivated, whereas (**C**) the patient with homozygous mutant (m/m) drug metabolism inactivates only 1% of the dose by the polymorphic pathway, yielding the three drug concentration-time curves. Pharmacological effects are further influenced by different genotypes of the drug receptor (blue lettering), which have different sensitivity to the medication, as depicted by the curves of drug concentration versus effects (middle). Patients with a wt/wt receptor genotype exhibit a greater effect at any given drug concentration in comparison to those with a wt/m receptor genotype, whereas those with m/m receptor genotypes are relatively refractory to drug effects at any plasma drug concentration. These two genetic polymorphisms (in drug metabolism and drug receptors) yield nine different theoretical patterns of drug effects (right). The therapeutic ratio (efficacy: toxicity) ranges from a favorable 75 in the patient with wt/wt genotypes for drug metabolism and drug receptors to <0.13 in the patient with m/m genotypes for drug metabolism and drug receptors.

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another that determines the sensitivity of the drug receptor. The polymorphic drug-metabolizing enzyme, which exhibits codominant inheritance (that is, three phenotypes), determines the plasma concentrations to which each individual is exposed, whereas the polymorphic receptor determines the nature of response at any given drug concentration. This example assumes that drug toxicity (Fig. 1, red lines) is determined by nonspecific effects or through receptors that do not exhibit functionally important genetic polymorphisms, although clearly toxicity can also be determined by genetic polymorphisms in drug receptors. Thus, the individual with homozygous wild-type drug-metabolizing enzymes and drug receptors (Fig. 1A) would have a high probability of therapeutic efficacy and a low probability of toxicity, in contrast to an individual with homozygous mutant genotypes for the drug-metabolizing enzyme and the drug receptor, in which the likelihood of efficacy is low and that of toxicity is high (Fig. 1C).

Such polygenic traits are more difficult to elucidate in clinical studies, especially when a medication's metabolic fate and mechanisms of action are poorly defined. However, biomedical research is rapidly defining the molecular mechanisms of pharmacologic effects, genetic determinants of disease pathogenesis, and functionally important polymorphisms in genes that govern drug metabolism and disposition. Moreover, the Human Genome Project, coupled with functional genomics and high-throughput screening methods, is providing powerful new tools for elucidating polygenic components of human health and disease. This has spawned the field of "pharmacogenomics", which aims to capitalize on these insights to discover new therapeutic targets and interventions and to elucidate the constellation of genes that determine the efficacy and toxicity of specific medications. In this context, pharmacogenomics refers to the entire spectrum of genes that determine drug behavior and sensitivity, whereas pharmacogenetics is often used to define the more narrow spectrum of inherited differences in drug metabolism and disposition, although this distinction is arbitrary and the two terms are now commonly used interchangeably. Ultimately, knowledge of the genetic basis for drug disposition and response should make it possible to select many medications and their dosages on the basis of each patient's inherited ability to metabolize, eliminate, and respond to specific drugs. Herein, we provide examples that illustrate the current status of such pharmacogenomic research and discuss the prospects for near-term advances in this field.

## Genetic Polymorphisms in Drug Metabolism and Disposition

Until recently, clinically important genetic polymorphisms in drug metabolism and disposition were typically discovered on the basis of phenotypic differences among individuals in the population (*8*), but the framework for discovery of pharmacogenetic traits is rapidly changing. With recent advances in molecular sequencing technology, gene polymorphisms [such as single-nucleotide polymorphisms (SNPs), and especially SNPs that occur in gene regulatory or coding regions (cSNPs)] may be the initiating discoveries, followed by biochemical and, ultimately, clinical studies to assess whether these genomic polymorphisms have phenotypic consequences in patients. This latter framework may permit the elucidation of polymorphisms in drug-metabolizing enzymes that have more subtle, yet clinically important consequences for interindividual variability in drug response. Such polymorphisms may or may not have clear clinical importance for affected medications, depending on the molecular basis of the polymorphism, the expression of other drug-metabolizing enzymes in the patient, the presence of concurrent medications or illnesses, and other polygenic clinical features that impact upon drug response. In Fig. 2, we have highlighted those drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences; however, almost every gene involved in drug metabolism is subject to common genetic polymorphisms that may contribute to interindividual variability in drug response. Table 1 provides examples of how these genetic polymorphisms can translate into clinically relevant inherited differences in drug disposition and effects, a comprehensive summary of which is available at www.sciencemag.org/feature/data/1044449.shl.

All pharmacogenetic polymorphisms studied to date differ in frequency among ethnic and racial groups. In fact, the slow acetylator phenotype was originally suspected to be genetically determined because of the difference in frequency of isoniazid-induced neuropathies observed in Japan versus those observed in the United States (*9*). The marked racial and ethnic diversity in the frequency of functional polymorphisms in drug- and xenobiotic-metabolizing enzymes dictates that race be considered in studies aimed at discovering whether specific genotypes or phenotypes are associated with disease risk or drug toxicity.

It is now well recognized that adverse drug reactions may be caused by specific drug-metabolizer phenotypes. This is illustrated by the severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase–deficient patients are treated with standard does of azathioprine or mercaptopurine (*6*). Another example is the slow acetylator phenotype that has been associated with hydralazine-induced lupus, isoniazid-induced neuropathies, dye-associated bladder cancer, and sulfonamide-induced hypersensitivity reactions (*9, 10*); in all cases, acetylation of a parent drug or an active metabolite is an inactivating pathway. *N*-Acetyltransferase is an enzyme that conju-

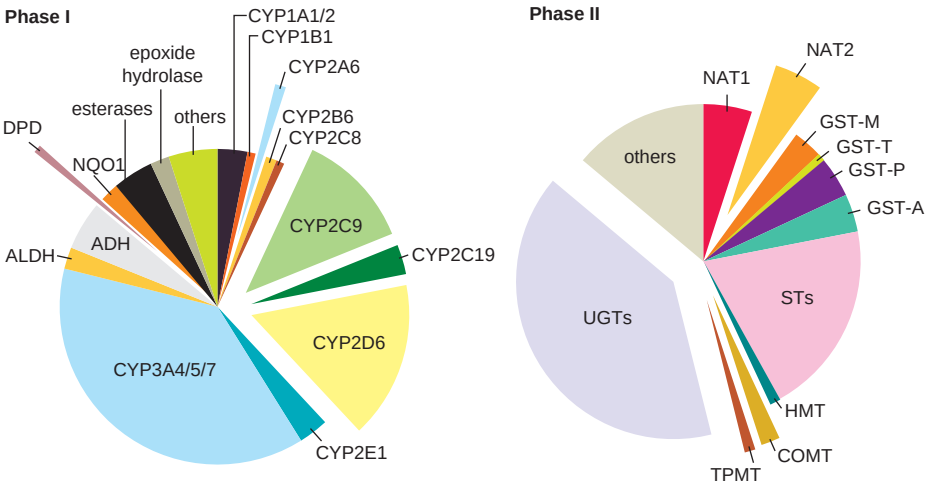


**Fig. 2.** Most drug-metabolizing enzymes exhibit clinically relevant genetic polymorphisms. Essentially all of the major human enzymes responsible for modification of functional groups [classified as phase I reactions (**left**)] or conjugation with endogenous substituents [classified as phase II reactions (**right**)] exhibit common polymorphisms at the genomic level; those enzyme polymorphisms that have already been associated with changes in drug effects are separated from the corresponding pie charts. The percentage of phase I and phase II metabolism of drugs that each enzyme contributes is estimated by the relative size of each section of the corresponding chart. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; NQO1, NADPH:quinone oxidoreductase or DT diaphorase; COMT, catechol *O*-methyltransferase; GST, glutathione *S*-transferase; HMT, histamine methyltransferase; NAT, *N*-acetyltransferase; STs, sulfotransferases; TPMT, thiopurine methyltransferase; UGTs, uridine 5′-triphosphate glucuronosyltransferases.

gates substrates with a more water-soluble small molecular moiety. Such conjugation reactions are frequently, but not always, detoxifying, in that they often "mask" a more reactive functional group and usually enhance urinary or biliary excretion of substrates. There are many examples in which the combination of a genetic defect in a conjugation pathway (Fig. 2, right), coupled with a wild-type phenotype for an oxidation pathway (Fig. 2, left), many of which can make substrates more reactive through the insertion of oxygen or other chemical modifications, results in a phenotype particularly predisposed to adverse effects from a medication or environmental substance. Alternatively, increased CYP1A activity (an enzyme catalyzing a phase I oxidation reaction), coupled with slow acetylation (a phase II conjugation reaction), resulted in less myelosuppression from the active metabolites of the anticancer agent amonafide (*11*). Because every individual represents a combination of drug-metabolizer phenotypes, given the large number of enzymes involved in drug metabolism, it is apparent that some individuals are destined to have unusual reactions to drugs or to combinations of drugs due to the coincident occurrence of multiple genetic defects in drug-metabolizing enzymes. Such an alignment of genotypes, particularly when coupled with polymorphisms in drug receptors, is likely to constitute part of the mechanism for so-called "idiosyncratic" drug reactions.

In addition to detoxifying and eliminating drugs and metabolites, drug-metabolizing enzymes are often required for activation of prodrugs. Many opioid analgesics are activated by CYP2D6 (*7*), rendering the 2 to 10% of the population who are homozygous for nonfunctional *CYP2D6* mutant alleles relatively resistant to opioid analgesic effects. It is thus not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed.

For many genetic polymorphisms of drug-metabolizing enzymes, there is no evident phenotype in the absence of a drug challenge, perhaps because these enzymes are not critical for metabolism of endogenous compounds in physiologically essential pathways. However, some drug-metabolism genotypes may result in a phenotype in the absence of drug; for example, it has been postulated that CYP2D6-poor metabolizers are less pain tolerant than extensive metabolizers because of a defect in synthesizing endogenous morphine (*12*) and that certain forms of dihydropyrimidine dehydrogenase deficiency are associated with mental retardation (*13*). Moreover, the risk of some cancers has been linked to polymorphisms in drug-metabolizing enzymes, which may be due to an impaired ability to inactivate exogenous or endogenous mutagenic molecules.

As depicted in Fig. 2, CYP3A4 is the human enzyme known to be involved in the metabolism of the largest number of medications. Thus far, no completely inactivating mutations have been discovered in the human *CYP3A4* gene, although a common polymorphism in the *CYP3A4* promoter has been recently described (*14*). For enzymes that apparently do not have critical endogenous substrates (for example, *CYP2C19*, *CYP2D6*, and *TPMT*), the molecular mechanisms of inactivation include splice site mutations resulting in exon skipping (for example, *CYP2C19*), microsatellite nucleotide repeats (for example, *CYP2D6*), gene duplication (for example, CYP2D6), point mutations resulting in early stop codons (for example, *CYP2D6*), amino acid substitutions that alter protein stability or catalytic activity (for example, *TPMT*, *NAT2*, *CYP2D6*, *CYP2C19*, and *CYP2C9*), or complete gene deletions (for example, *GSTM1* and *CYP2D6*). It is remarkable that even for rare phenotypes such as thiopurine methyltransferase deficiency (which occurs in only 1 in 300 individuals), a small number of recurring mutations have been shown to account for most of the mutant alleles in humans (*6*). For this and other drug-metabolizing genes, the frequency of SNPs and other genetic defects appears to be more common than the frequency of "1 per 1000 base pairs" that is cited for the human genome. Perhaps it is because some "drug"-metabolizing enzymes are dispensable or redundant with other enzymes (such as CYP2D6 and CYP2C19) that genetic polymorphisms of drug-metabolizing enzymes are so common.

## Genetic Polymorphisms in Drug Transporters

Although passive diffusion accounts for cellular uptake of some drugs and metabolites, increased emphasis (*15*) is being placed on the role of membrane transporters in absorption of oral medications across the gastrointestinal tract; excretion into the bile and urine; distribution into "therapeutic sanctuaries," such as the brain and testes; and transport into sites of action, such as cardiovascular tissue, tumor cells, and infectious microorganisms. It has been proposed that some of these transporters, such as *P*-glycoprotein, may not be essential for viability, because

**Table 1.** Examples of clinically relevant genetic polymorphisms influencing drug metabolism and effects. A comprehensive listing is available at www.sciencemag.org/feature/data/1044449.shl.

| Gene | Medications | Drug effect linked to polymorphism | References |
|---|---|---|---|
| | *Drug-metabolizing enzymes* | | |
| CYP2C9 | Tolbutamide, warfarin, phenytoin, nonsteroidal anti-inflammatories | Anticoagulant effect of warfarin | (*32*) |
| CYP2D6 | Beta blockers, antidepressants, antipsychotics, codeine, debrisoquin, dextromethorphan, encainide, flecainide, guanoxan, methoxyamphetamine, *N*-propylajmaline, perhexiline, phenacetin, phenformin, propafenone, sparteine | Tardive dyskinesia from antipsychotics; narcotic side effects, efficacy, and dependence; imipramine dose requirement; beta-blocker effect | (*6, 12, 33*) |
| Dihydropyrimidine dehydrogenase | Fluorouracil | Fluorouracil neurotoxicity | (*13*) |
| Thiopurine methyltransferase | Mercaptopurine, thioguanine, azathioprine | Thiopurine toxicity and efficacy; risk of second cancers | (*6, 34*) |
| | *Drug targets* | | |
| ACE | Enalapril, lisinopril, captopril | Renoprotective effects, cardiac indices, blood pressure, immunoglobulin A nephropathy | (*18, 21*) |
| Potassium channels | | | |
| HERG | Quinidine | Drug-induced long QT syndrome | (*35*) |
| | Cisapride | Drug-induced torsade de pointes | |
| KvLQT1 | Terfenadine, disopyramide, meflaquine | Drug-induced long QT syndrome | |
| hKCNE2 | Clarithromycin | Drug-induced arrhythmia | (*26*) |

knockout mice appear normal until challenged with xenobiotics. However, other transporters are likely to play critical roles in transport of endogenous substances. Although polymorphisms in *P*-glycoprotein have been reported (*16*), and such variation may have functional importance for drug absorption and elimination, the clinical relevance of polymorphisms in drug transporters has not yet been fully elucidated.

## Genetic Polymorphisms in Drug Targets

Most drugs interact with specific target proteins to exert their pharmacological effects, such as receptors, enzymes, or proteins involved in signal transduction, cell cycle control, or many other cellular events. Molecular studies have revealed that many of the genes encoding these drug targets exhibit genetic polymorphism, which in many cases alters their sensitivity to specific medications. Such examples include polymorphisms in β-adrenergic receptors and their sensitivity to β-agonists in asthmatics (*17*), angiotensin converting enzyme (ACE) and its sensitivity to ACE inhibitors (*18*), angiotensin II T1 receptor and vascular reactivity to phenylephrine (*19*) or response to ACE inhibitors (*20*), sulfonylurea receptor and responsiveness to sulfonylurea hypoglycemic agents (*21*), and 5-hydroxtryptamine receptor and response to neuroleptics such as clozapine (*22*). In addition, genetic polymorphisms that underlie disease pathogenesis can also be major determinants of drug efficacy, such as mutations in the apolipoprotein E gene and responsiveness of patients with Alzheimer's disease to tacrine therapy (*23*) or cholesteryl ester transfer protein polymorphisms and efficacy of pravastatin therapy in patients with coronary atherosclerosis (*24*). Finally, the risk of adverse drug effects has been linked to genetic polymorphisms that predispose to toxicity, such as dopamine D3 receptor polymorphism and the risk of drug-induced tardive dyskinesia (*25*), potassium channel mutations and drug-induced dysrhythmias (*26*), and polymorphism in the ryanodine receptor and anesthesia-induced malignant hyperthermia (*27*). Polymorphisms in genes of pathogenic agents (human immunodeficiency virus, bacteria, tuberculosis, and others) are another important source of genetic variation in drug sensitivity, but this review focuses only on polymorphisms in human genes that determine an individual's response to specific medications.

Table 1 provides examples of genetic polymorphisms in drug targets that have been linked to altered drug sensitivity. It is anticipated that ongoing studies will rapidly expand the number of such pharmacogenomic relations. Furthermore, these examples represent monogenic determinants of drug effects, which are the easiest to recognize in population studies. It is likely, however, that drug response is often a polygenic trait, in which case more comprehensive studies will be required to define pharmacogenomic traits that are determined by multiple polymorphic genes. It should also be recognized that not all studies have reached the same conclusions about the effects of genetic polymorphisms on drug response [for example, not all studies of ACE polymorphisms have found a relation with response to ACE inhibitors (*18*)]. Such discordant results may be due to a number of factors, including the use of different end points in assessing response, the heterogeneous nature of diseases studied, and the polygenic nature of many drug effects. The rapidly expanding knowledge of the human genome, coupled with automated methods for detecting gene polymorphisms, provides the tools needed to elucidate these polygenic determinants of drug effects, thus fueling the burgeoning field of pharmacogenomics.

## Relevance to Drug Discovery and Clinical Therapeutics

Substantial investments are being made within the pharmaceutical and biotechnology industries to use genomic strategies for the discovery of novel therapeutic targets (*28*). It is anticipated that, over the next decade, the Human Genome Project, coupled with DNA array technology, high-throughput screening systems, and advanced bioinformatics, will permit rapid elucidation of complex genetic components of human health and disease. Common polymorphisms in drug targets dictate that DNA sequence variations be taken into account in the genomic screening processes aimed at new drug development. This will provide new insights for the development of medications that target critical pathways in disease pathogenesis and medications that can be used to prevent diseases in individuals who are genetically predisposed to them.

Such pharmacogenomic studies should also permit the development of therapeutic agents targeted for specific, but genetically identifiable, subgroups of the population. This represents a migration from the traditional strategy of trying to develop medications that are safe and effective for every member of the population, a strategy that aims to provide a marketing bonanza but one that is a pharmacological long shot because of highly potent medications, genetically diverse patients, and diseases that have heterogeneous subtypes. Although debate about the wisdom of developing medications for only a subset of the population remains within the pharmaceutical industry (*28*), it is clear that science and technology will soon make it feasible to use molecular diagnostics to more precisely select medications and dosages that are optimal for individual patients (*29*). In this regard, automated systems are being developed to determine an individual's genotype for polymorphic genes that are known to be involved in the pathogenesis of their dis-

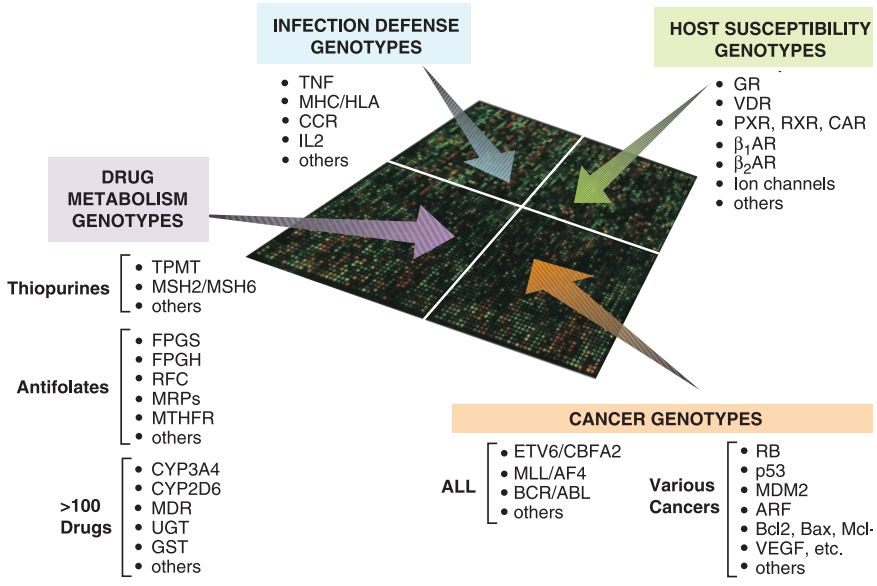


**Fig. 3.** Molecular diagnostics of pharmacogenomic traits. DNA arrays are being made for automated, high-throughput detection of functionally important mutations in genes that are important determinants of drug effects, such as drug-metabolizing enzymes, drug targets (receptors), disease pathogenesis, and other polymorphic genes that influence an individual's susceptibility to drug toxicities or environmental exposures (such as pathogens, carcinogens, and others). This figure exemplifies components of a potential diagnostic DNA array for genes that could influence a patient's response to chemotherapy for acute lymphoblastic leukemia, including genes that determine drug metabolism, disease sensitivity, and the risk of adverse effects of treatment (cardiovascular or endocrine toxicities, infections, and so forth).

ease, in the metabolism and disposition of medications, and in the targets of drug therapy. Such diagnostics, which need be performed only once for each battery of genes tested, can then become the blueprint for individualizing drug therapy. This is illustrated in Fig. 3, which depicts various genes that could be genotyped to guide the selection and dosing of chemotherapy for a patient with acute lymphoblastic leukemia (ALL). It is already known that genetic polymorphisms in drug-metabolizing enzymes can have a profound effect on toxicity and efficacy of medications used to treat ALL (*6*) and that individualizing drug dosages can improve clinical outcome (*30*). It has also been established that the genotype of leukemic lymphoblasts is an important prognostic variable that can be used to guide the intensity of treatment (*31*). Furthermore, genetic polymorphisms are also known to exist for cytokines and other determinants of host susceptibility to pathogens, and polymorphisms in cardiovascular, endocrine, and other receptors may be important determinants of an individual's susceptibility to drug toxicity. Putting all of these molecular diagnostics on an "ALL chip" would provide the basis for rapidly and objectively selecting therapy for each patient. These examples represent our current, relatively poor, understanding of genetic determinants of leukemia therapy and host sensitivity to treatment; ongoing studies will provide important insights that should substantially enhance the utility of such pharmacogenomic strategies for ALL and many other human illnesses.

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