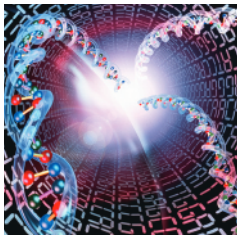
Role of Pharmacogenomic Biomarkers In Predicting and Improving Drug Response

Part 1: The Clinical Significance of Pharmacogenetic Variants

C. Lee Ventola, MS



This is the first in a series of two articles about pharmacogenomics and drug response. Part 2 will discuss the challenges that impede the clinical use of pharmacogenomics.

Introduction

A current focus of pharmacogenomic research is to explore the effect of inter-individual genetic differences on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drug treatments.[1] The ultimate goal of these efforts is to develop personalized, genetic-based strategies that will optimize therapeutic outcomes.[1] Gene–drug associations have been identified for anticonvulsant, anti-infective, cancer, cardiovascular, opioid, proton-pump inhibitor, and psychotropic drugs, as well as other types of treatments.[1,3–8] Many genetic variants have been identified that are known to alter cytochrome P450 (CYP) enzymes and drug receptors, transporters, and targets.[2,3] These modifications can greatly influence pharmacokinetics, dose requirements, and other factors that affect therapeutic outcomes.[1–4] The clinical application of such pharmacogenetic findings holds great promise in improving drug efficacy and safety.[1]

How Do Pharmacogenomics and Pharmacogenetics Differ?

Both pharmacogenomics and pharmacogenetics concern the effect of genetic variations on drug metabolism and response, but these fields do differ.[9] Pharmacogenomics is the "genome-wide analysis of genetic determinants of drug-metabolizing enzymes, receptors, transporters, and targets that influence therapeutic efficacy and safety and drug-related phenotypes."[3,4,6,9,10] Pharmacogenomic research involves scanning the whole genome to find single-nucleotide polymorphisms (SNPs) that might be associated with drug response without necessarily knowing the specific function of the identified SNPs.[2] Whereas pharmacogenomics involves the study of genes in all chromosomes,[3,10] pharmacogenetics is the study of specific SNPs in distinct genes with known functions that are plausibly connected to drug response.

Although the two terms are often used interchangeably, pharmacogenomics is becoming the preferred term to describe genetic variations—either inherited (germline), acquired (somatic), or both—that influence drug response.[1]

Goals of Pharmacogenomics and Pharmacogenetics

Prior to the introduction of pharmacogenomics, treatment choices were traditionally made based on a patient's medical history and pathology.[7] Possible influences on drug response that are usually considered when making treatment decisions include age, sex, disease, environmental factors, diet, and drug interactions.[3,7] Dose adjustments are typically made based on a patient's age, sex, organ function, body weight, and body surface area.[7] However, even when these factors are taken into account, drug response still often varies among patients, ranging from positive outcomes to fatal adverse reactions.[7]

These long-established clinical parameters will continue to be used to guide drug treatment.[6] However, they don't directly consider genetic factors, which can account for 20% to 40% of inter-individual differences in drug metabolism and response.[6] In fact, for certain drugs or drug classes, genetic factors have been shown to be the most important influence on drug treatment outcomes.[6]

Therefore, the goal of pharmacogenomic and pharmacogenetic research is to apply current knowledge about genetic variants that influence drug response to develop personalized treatment strategies that maximize therapeutic efficacy and safety.[1,5–7] Personalized drug therapy is especially desirable when prescribing a drug with a narrow therapeutic index or when drug toxicity can be life-threatening.[5,7] For example, antineoplastic, anticoagulant, and anti-HIV therapies are often administered at maximally tolerated doses that are typically chosen from population averages.[5] However, this approach can result in toxicity in up to one-third of patients, and a significant portion of the people treated can exhibit poor or no response.[5]

Genetic factors account for 20% to 40% of inter-individual differences in metabolism and response. For certain drugs or drug classes, they are the most important influence on treatment outcomes.

Severe adverse drug reactions are one of the most common reasons for hospital admissions in the U.S.[6,7] Adverse drug reactions rank as the fourth leading cause of death in the U.S. and are responsible for 100,000 deaths annually.[6,7] Genetic testing for drug response is expected to reduce the risk of hospitalization by as much as 30%.[5] To this end, multidisciplinary teams of laboratory, clinical, and computational researchers are working together to personalize drug treatment by incorporating an individual's genetic information (both germline and somatic) into existing prescribing models.[7] A patient's genome needs to be identified only once in a lifetime, which makes pharmacogenetic screening a potentially very potent, cost-effective diagnostic tool.[1]

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The author is a consultant medical writer living in New Jersey.

Types of Genetic Variants That Can Influence Drug Response

The number of pharmacogenetic associations known to affect drug response has steadily increased over the years.[11] Genetic polymorphisms have been identified for many proteins that are significant in clinical pharmacology, including enzymes, drug receptors, transporters, and targets.[2,3] These polymorphisms can cause alterations in the amount, structure, binding, and/or function of these proteins, affecting how drugs interact with them.[2,3] Genetic variants can alter the pharmacokinetics and pharmacodynamics of a drug, potentially affecting both drug efficacy and toxicity.[4] Evidence indicates that genetic factors can account for an estimated 20% to 95% of drug metabolism and response.[1]

The majority of observed DNA sequence variations are due to SNPs, which are single base-pair substitution mutations.[11] These occur every 100 to 300 base pairs and account for 90% of all human genetic variations.[11] The location of the SNPs in relation to a particular gene determines whether or not the normal function of a gene is affected.[11] The net effect of an SNP on gene function can also depend on whether one or both copies of a gene are affected by a variant; therefore, one of the aims of pharmacogenetic testing is to identify heterozygous and homozygous SNPs.[11]

Genetic variation can also occur in "non-SNP" polymorphisms, better known as structural variations (SVs).[9] SVs consist of small (fewer than 10 base pairs) insertions or deletions (indels), copy number variations (CNVs), and inversions.[10] These genetic modifications occur less frequently than SNPs but have greater repercussions because they encompass larger regions of genomic variation than SNPs do.[1,10] For example, if an indel occurs in the coding region of a gene, this can lead to completely aberrant, nonfunctional proteins.[1,10] Both SNPs and SVs are thought to play a role to varying degrees with respect to individual phenotypic drug response outcomes, such as drug sensitivity, resistance, and toxicity.[1]

Effect of Genetic Variants on Pharmacokinetics And Pharmacodynamics

CYP450 enzymes, each of which is coded for by a different gene, are responsible for metabolizing the majority of drugs.[2,3,6,10] Genetic polymorphisms identified in *CYP450* genes affect the metabolism of up to 25% of all drug therapies.[2,3,6] Polymorphisms in the genetic coding sequences for these enzymes can influence drug response, causing it to be normal, increased, reduced, or even completely neutralized.[10] For example, genetic variations in *CYP2D6* and other genes that encode for drug-metabolizing enzymes (DMEs) have been correlated with four different metabolism phenotypes: ultrarapid metabolizers (UMs), normal/extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs).[3,9] Now that DNA-based CYP450 enzyme tests are clinically available, genetic screening can identify these metabolism phenotypes in individuals.[9]

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Polymorphic variant alleles of many important *CYP450* genes have been discovered in different populations.[9] Notable discoveries include two enzymes from the *CYP2C* subfamily: *CYP2C9* and *CYP2C19*.[10] The enzyme coded for by the *CYP2C9* allele metabolizes many clinically relevant drugs, including warfarin, phenytoin (Dilantin, Pfizer), tolbutamide, losartan (Cozaar, Merck), and others.[9] Like other *CYP450* genes, the *CYP2C9* gene is highly polymorphic. Genetic variations of the *CYP2C9* allele have been strongly associated with inter-individual warfarin dosing variability.[5,]

At least 27 variant alleles for *CYP2C19* have also been identified, with the most extensively described being *CYP2C19*2* and *CYP2C19*3*.[9] The *CYP2C19*2* allele was originally associated with impaired mephenytoin metabolism, and it has also since been linked to a reduction in active clopidogrel metabolites.[9] This causes higher platelet aggregation and adverse clinical outcomes in certain clopidogrel-treated, cardiovascular patient populations compared with non-carriers.[9] With respect to *CYP2C19*2*, a splicing defect in exon 5 occurs, resulting in early termination of protein synthesis.[7] Similarly, *CYP2C19*3* is a premature stop codon SNP, which results in a truncated protein.[3] The functional effect of these polymorphisms is a complete loss of enzyme activity.[3,9] Other *CYP2C19* alleles also result in a loss (*CYP2C19*4–*8*), reduced (*CYP2C19*9*, **10*, and **12*), or increased (*CYP2C19*17*) metabolic enzyme activity.[3] Variation in genes coding for drug metabolism enzyme aren't the sole determinant of drug response.[9] Polymorphisms in genes that code for drug receptors, transporters, and targets also play a role.[9] For example, a variant allele in the solute carrier organic anion transporter family member *1B1* (*SLCO1B1)* gene has been associated with statin-induced myalgia.[9] A common variant in the *VKORC1* gene (vitamin K epoxide reductase complex subunit 1), which encodes a target of warfarin, has also been strongly associated with inter-individual dosing variability for that drug.[5,9]

Specific Pharmacogenetic Associations Known to Alter Drug Response

Genetic Variants and Response to Anticonvulsant Drugs

Carbamazepine has been linked to dose-dependent side effects as well as life-threatening idiosyncratic adverse reactions.[3] It is metabolized primarily by enzymes encoded by the *CYP3A4* gene to the active metabolite, carbamazepine-10,11-epoxide.[3]

> Variation in genes coding for drug metabolism enzyme aren't the sole determinant of drug response. Polymorphisms in genes that code for drug receptors, transporters, and targets also play a role.

The human leukocyte antigen *(HLA)* gene has been a primary focus in the study of hypersensitivity and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) reactions that occur in response to carbamazepine treatment, which tend to be familial.[3] Investigators discovered an association between the *HLA-B*1502* allele and the risk of SJS/TEN, particularly in Asians who are prescribed carbamazepine.[3] In a landmark study of 44 Han Chinese patients, a 100% association between the *HLA-B*1502* allele and carbamazepine-induced SJS/TEN was observed.[3] However, this allele has not been shown to increase the risk for carbamazepine-induced hypersensitivity in Caucasians.[3]

Other *HLA* alleles have been identified as potential markers for carbamazepine-induced hypersensitivity reactions in other populations.[3] For example, the *HLA-A*3101* allele has been associated with carbamazepine-induced hypersensitivity reactions in Japanese and European populations.[3] In addition, the *HLA-B*1511* allele was discovered to be a risk factor for carbamazepine-induced SJS/TEN in Japanese patients.[3] Another study reported an association between the *HLA-B*1518*, *HLA-B*5901*, and *HLA-C*0704* alleles and severe cutaneous adverse drug reactions.[3]

> Physicians could avoid many adverse drug reactions if they were capable of predicting an individual's response to treatment.

Before carbamazepine treatment is initiated in high-risk patients, genetic testing is recommended.[3] In 2007, the FDA recommended that all patients of Asian ancestry be screened for the *HLA-B*1502* allele before they begin carbamazepine therapy.[3] This recommendation is stated in the boxed warning section of the carbamazepine product information.[3]

Table 1 includes a comprehensive list of drug labels that have been revised by the FDA to include information about pharmacogenomic biomarkers.[12]

Genetic Variants and Response to Anti-infective Drugs

More than 170 million people worldwide are chronically infected with the hepatitis C virus (HCV). Complications of this infection include liver cirrhosis, hepatic injury, and hepatic fibrosis.[5] Over the previous decade, the standard of care for HCV has been 24 to 48 weeks of polyethylene glycol (PEG-interferon, or pegylated interferon) treatment, either alone or in combination with ribavirin.[5] Patients who respond to this treatment often achieve a sustained virological response, which is associated with a good quality of life.[5]

Several independent genome-wide association studies (GWAS) demonstrated that a variant in the gene encoding interleukin-28B (IL28B) is associated with this positive treatment response.[5] This genetic variant also predicted treatment response in patients with HCV who were co-infected with HIV.[5] Although the package insert for PEG-interferon has been revised to include information regarding this *IL28B* variant, a specific recommendation with respect to screening patients before initiating treatment has not been included.[12]

Physicians could avoid many adverse drug reactions if they were capable of predicting an individual's response to treatment.[6] Abacavir, a nucleoside reverse transcriptase inhibitor (NRTI) used to treat AIDS, is known to cause a hypersensitivity reaction in 5% to 8% of patients.[6] The reaction can include fever, rash, and gastrointestinal or respiratory symptoms, which often lead to treatment discontinuation.[6] *HLA-B*5701*, a member of the *HLA* gene family that codes for proteins which play a critical role in regulating immune system response, has been associated with abacavir hypersensitivity.[6]

In 2008, the FDA revised the product information for abacavir to include a boxed warning regarding the association of *HLA-B*5701* with abacavir hypersensitivity.[13] The prescribing information now recommends that patients be prescreened for the *HLA-B*5701* allele prior to initiation or re-treatment with abacavir or abacavir-containing medications.[13] The prescribing information also advises that abacavir treatment should not be initiated in patients who are positive for this allele except under extraordinary circumstances.[13]

Genetic Variants and Response to Cancer Drugs

Many early successes in pharmacogenomic research took place in oncology, where somatic genetic changes in tumors were found to have more of an effect on drug efficacy compared with variations in an individual's germline DNA.[4]

Tumor cells carry the same germline genetic polymorphisms that normal cells do; however, the genetic instability of malignant cells can produce a high incidence of additional mutations, increase the copy number of inherited variants, or even repress gene expression.[1,4] These genetic changes can increase copies of genes encoding DMEs or drug transporters, which can lead to alterations in the disposition of active drugs at the site of the tumor.[1]

Much knowledge regarding somatic genetic alterations that influence response to cancer therapies has been gathered over the past several decades. This information has led to the development of many targeted cancer treatments.[1] Genetic analysis of tumors can help predict therapeutic benefits (or lack thereof) of such targeted biologics as trastuzumab (Herceptin, Genentech) for ERBB2 (HER2)-amplified breast cancers; erlotinib (e.g., Tarceva, OSI/Genentech) for epidermal growth factor receptor (EGFR)–overexpressing lung cancers; or imatinib (e.g., Gleevec, Novartis) for Philadelphia chromosome–positive chronic myelogenous leukemia (CML).[4]

Somatic genetic mutations in tumors can also help predict resistance to treatment, as has been observed in colorectal cancers, in which activating mutations in *KRAS* (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) are known to be a predictive marker for resistance to the EGFR-specific monoclonal antibodies cetuximab (e.g., Erbitux, Bristol-Myers Squibb/ImClone) and panitumumab (e.g., Vectibix, Amgen).[4] The FDA has revised the drug labels for cetuximab and panitumumab to include this information regarding *KRAS* mutations.[1]

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One pharmacogenomic study estimated that genetic factors could determine more than 40% of the susceptibility to cisplatin-induced cytotoxicity.[7] Cisplatin is a platinating agent used to treat various types of cancers, including lung cancer and lymphoma.[6] In another study, an SNP in a *NRG3* gene (which has never been linked to cancer) was found to be associated with cellular sensitivity to platinum agents; this association was replicated in ovarian cancer patients who underwent platinum-based therapy.[7] These findings suggest that sensitivity to the cytotoxic effects of chemotherapeutic agents could be under substantial genetic influence.[7]

Genetic factors can also predict tolerance to cancer treatments. For example, polymorphisms in *SLCO1B1* have also been associated with methotrexate-related gastrointestinal

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Table 1 Pharmacogenomic Biomarkers in Drug Labels

This table lists FDA-approved drugs with labels that have been revised to include pharmacogenomic biomarker information. The revisions describe the effect of these biomarkers on drug exposure and clinical response variability; risk of adverse events; genotype-specific dosing; mechanisms of drug action; and polymorphic gene drug targets and disposition. Some, but not all, of the revised labels include specific treatment approaches to be taken in response to pharmacogenetic data. For more complete information, please consult the relevant drug labels.

Drug	Therapeutic Area	Biomarker	Label Sections
Abacavir	Antivirals	HLA-B*5701	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Ado-trastuzumab emtansine	Oncology	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Aripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration
Arsenic trioxide	Oncology	PML/RARα	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings
Atomoxetine	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Atorvastatin	Metabolic and Endocrinology	LDL receptor	Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Azathioprine	Rheumatology	TPMT	Dosage and Administration, Warnings and Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology
Boceprevir	Antivirals	IL28B	Clinical Pharmacology
Brentuximab vedotin	Oncology	CD30	Indications and Usage, Description, Clinical Pharmacology
Busulfan	Oncology	Ph Chromosome	Clinical Studies
Capecitabine	Oncology	DPD	Contraindications, Precautions, Patient Information
Carbamazepine	Neurology	HLA-B*1502	Boxed Warning, Warnings and Precautions
Carisoprodol	Musculoskeletal	CYP2C19	Clinical Pharmacology, Special Populations
Carvedilol	Cardiovascular	CYP2D6	Drug Interactions, Clinical Pharmacology
Celecoxib	Analgesics	CYP2C9	Dosage and Administration, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
Cetuximab (1)	Oncology	EGFR	Indications and Usage, Warnings and Precautions, Description, Clinical Pharmacology, Clinical Studies
Cetuximab (2)	Oncology	KRAS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cevimeline	Dermatology and Dental	CYP2D6	Drug Interactions
Chlordiazepoxide and amitriptyline	Psychiatry	CYP2D6	Precautions
Chloroquine	Anti-infectives	G6PD	Precautions
Cisplatin	Oncology	TPMT	Clinical Pharmacology, Warnings, Precautions
Citalopram (1)	Psychiatry	CYP2C19	Drug Interactions, Warnings
Citalopram (2)	Psychiatry	CYP2D6	Drug Interactions
Clobazam	Neurology	CYP2C19	Clinical Pharmacology, Dosage and Administration, Use in Specific Populations
Clomipramine	Psychiatry	CYP2D6	Drug Interactions
Clopidogrel	Cardiovascular	CYP2C19	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Clozapine	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology

Pharmacogenomic Biomarkers, Part 1: Pharmacogenetic Variants

Drug	Therapeutic Area	Biomarker	Label Sections
Codeine	Analgesics	CYP2D6	Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology
Crizotinib	Oncology	ALK	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Dapsone (1)	Dermatology	G6PD	Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Patient Counseling Information
Dapsone (2)	Anti-infectives	G6PD	Precautions, Adverse Reactions, Overdosage
Dasatinib	Oncology	Ph Chromosome	Indications and Usage, Clinical Studies, Patient Counseling Information
Denileukin diftitox	Oncology	CD25	Indications and Usage, Warnings and Precautions, Clinical Studies
Desipramine	Psychiatry	CYP2D6	Drug Interactions
Dexlansoprazole (1)	Gastroenterology	CYP2C19	Clinical Pharmacology, Drug Interactions
Dexlansoprazole (2)	Gastroenterology	CYP1A2	Clinical Pharmacology
Dextromethorphan and quinidine	Neurology	CYP2D6	Clinical Pharmacology, Warnings and Precautions
Diazepam	Psychiatry	CYP2C19	Drug Interactions, Clinical Pharmacology
Doxepin	Psychiatry	CYP2D6	Precautions
Drospirenone and ethinyl estradiol	Reproductive	CYP2C19	Precautions, Drug Interactions
Eltrombopag (1)	Hematology	Factor V Leiden (FV)	Warnings and Precautions
Eltrombopag (2)	Hematology	Antithrombin III deficiency (SERPINC1)	Warnings and Precautions
Erlotinib	Oncology	EGFR	Clinical Pharmacology
Esomeprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Everolimus	Oncology	ERBB2 (HER2)	Indications and Usage, Boxed Warning, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Exemestane	Oncology	ER &/ PGR	Indications and Usage, Dosage and Administration, Clinical Studies, Clinical Pharmacology
Fluorouracil (1)	Dermatology	DPD	Contraindications, Warnings
Fluorouracil (2)	Oncology	DPD	Warnings
Fluoxetine	Psychiatry	CYP2D6	Warnings, Precautions, Clinical Pharmacology
Fluoxetine and olanzapine	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Flurbiprofen	Rheumatology	CYP2C9	Clinical Pharmacology, Special Populations
Fluvoxamine	Psychiatry	CYP2D6	Drug Interactions
Fulvestrant	Oncology	ER	Indications and Usage, Patient Counseling Information
Galantamine	Neurology	CYP2D6	Special Populations
Gefitinib	Oncology	EGFR	Clinical Pharmacology
Iloperidone	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration, Drug Interactions, Specific Populations, Warnings and Precautions
Imatinib (1)	Oncology	C-Kit	Indications and Usage, Dosage and Administration Clinical Pharmacology, Clinical Studies
Imatinib (2)	Oncology	Ph Chromosome	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies

Pharmacogenomic Biomarkers, Part 1: Pharmacogenetic Variants

Drug	Therapeutic Area	Biomarker	Label Sections
Imatinib (3)	Oncology	PDGFR	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib (4)	Oncology	FIP1L1-PDGFRα	Indications and Usage, Dosage and Administration, Clinical Studies
Imipramine	Psychiatry	CYP2D6	Drug Interactions
Indacaterol	Pulmonary	UGT1A1	Clinical Pharmacology
Irinotecan	Oncology	UGT1A1	Dosage and Administration, Warnings, Clinical Pharmacology
Isosorbide and hydralazine	Cardiovascular	NAT1; NAT2	Clinical Pharmacology
Ivacaftor	Pulmonary	CFTR (G551D)	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Lansoprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Lapatinib	Oncology	ERBB2 (HER2)	Indications and Usage, Clinical Pharmacology, Patient Counseling Information
Lenalidomide	Hematology	Chromosome 5q	Boxed Warning, Indications and Usage, Clinical Studies, Patient Counseling
Letrozole	Oncology	ER &/ PGR	Indications and Usage, Adverse Reactions, Clinical Studies, Clinical Pharmacology
Maraviroc	Antivirals	CCR5	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Mercaptopurine	Oncology	TPMT	Dosage and Administration, Contraindications, Precautions, Adverse Reactions, Clinical Pharmacology
Metoprolol	Cardiovascular	CYP2D6	Precautions, Clinical Pharmacology
Modafinil	Psychiatry	CYP2D6	Drug Interactions
Mycophenolic acid	Transplantation	HGPRT	Precautions
Nefazodone	Psychiatry	CYP2D6	Drug Interactions
Nilotinib (1)	Oncology	Ph Chromosome	Indications and Usage, Patient Counseling Information
Nilotinib (2)	Oncology	UGT1A1	Warnings and Precautions, Clinical Pharmacology
Nortriptyline	Psychiatry	CYP2D6	Drug Interactions
Omeprazole	Gastroenterology	CYP2C19	Dosage and Administration, Warnings and Precautions, Drug Interactions
Panitumumab (1)	Oncology	EGFR	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Panitumumab (2)	Oncology	KRAS	Indications and Usage, Clinical Pharmacology, Clinical Studies
Pantoprazole	Gastroenterology	CYP2C19	Clinical Pharmacology, Drug Interactions, Special Populations
Paroxetine	Psychiatry	CYP2D6	Clinical Pharmacology, Drug Interactions
PEG-interferon alfa-2b	Antivirals	IL28B	Clinical Pharmacology
Perphenazine	Psychiatry	CYP2D6	Clinical Pharmacology, Drug Interactions
Pertuzumab	Oncology	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Studies, Clinical Pharmacology
Phenytoin	Neurology	HLA-B*1502	Warnings
Pimozide	Psychiatry	CYP2D6	Warnings, Precautions, Contraindications, Dosage and Administration
Prasugrel	Cardiovascular	CYP2C19	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Pravastatin	Metabolic and Endocrinology	APOE2	Clinical Studies, Use in Specific Populations
Propafenone	Cardiovascular	CYP2D6	Clinical Pharmacology
Propranolol	Cardiovascular	CYP2D6	Precautions, Drug Interactions, Clinical Pharmacology

Drug	Therapeutic Area	Biomarker	Label Sections
Protriptyline	Psychiatry	CYP2D6	Precautions
Quinidine	Antiarrhythmics	CYP2D6	Precautions
Rabeprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Rasburicase	Oncology	G6PD	Boxed Warning, Contraindications
Rifampin, isoniazid, and pyrazinamide	Anti-infectives	NAT1; NAT2	Adverse Reactions, Clinical Pharmacology
Risperidone	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Sodium phenylacetate and sodium benzoate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Indications and Usage, Description, Clinical Pharmacology
Sodium phenylbutyrate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Indications and Usage, Dosage and Administration, Nutritional Management
Tamoxifen (1)	Oncology	ER	Indications and Usage, Precautions, Medication Guide
Tamoxifen (2)	Oncology	Factor V Leiden (FV)	Warnings
Tamoxifen (3)	Oncology	Prothrombin mutations (F2)	Warnings
Telaprevir	Antivirals	IL28B	Clinical Pharmacology
Terbinafine	Antifungals	CYP2D6	Drug Interactions
Tetrabenazine	Neurology	CYP2D6	Dosage and Administration, Warnings, Clinical Pharmacology
Thioguanine	Oncology	TPMT	Dosage and Administration, Precautions, Warnings
Thioridazine	Psychiatry	CYP2D6	Precautions, Warnings, Contraindications
Ticagrelor	Cardiovascular	CYP2C19	Clinical Studies
Tolterodine	Reproductive and Urologic	CYP2D6	Clinical Pharmacology, Drug Interactions, Warnings and Precautions
Tositumomab	Oncology	CD20 antigen	Indications and Usage, Clinical Pharmacology
Tramadol and acetaminophen	Analgesics	CYP2D6	Clinical Pharmacology
Trastuzumab	Oncology	ERBB2 (HER2)	Indications and Usage, Precautions, Clinical Pharmacology
Tretinoin	Oncology	PML/RARα	Boxed Warning, Dosage and Administration, Precautions
Trimipramine	Psychiatry	CYP2D6	Drug Interactions
Valproic acid	Psychiatry	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Contraindications, Precautions, Adverse Reactions
Vemurafenib	Oncology	BRAF	Indications and Usage, Warning and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Venlafaxine	Psychiatry	CYP2D6	Drug Interactions
Voriconazole	Antifungals	CYP2C19	Clinical Pharmacology, Drug Interactions
Warfarin (1)	Hematology	CYP2C9	Dosage and Administration, Precautions, Clinical Pharmacology
Warfarin (2)	Hematology	VKORC1	Dosage and Administration, Precautions, Clinical Pharmacology

Adapted from the FDA. Updated June 19, 2013.[12]

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toxicity and disposition of the cyclin-dependent kinase inhibitor flavopiridol.[1]

Genetic Variants and Response to Cardiovascular Drugs

The appropriate dose of warfarin can vary by as much as 10-fold among patients.[4] Genetic variations in three genes—CYP2C9, VKORC1, and CYP4F2—contribute significantly to this variability.[4] Approximately 550,000 genetic polymorphisms have been evaluated. The most significant effect was found for *VKORC1*, with a more moderate association found for the *CYP2C9* variants rs4917639 (*CYP2C9*2)* and rs1057910 (*CYP2C9**3).[1]

VKORC1 codes for the vitamin K epoxide reductase protein, the target enzyme for warfarin.[1] Variants in *VKORC1* have been significantly associated with warfarin sensitivity and reduced dose requirements.[1] The primary enzyme involved in the metabolism of *S*-warfarin (a more potent form of warfarin), which is primarily responsible for anticoagulation, is encoded by the *CYP2C9*1* gene.[1,4] The *CYP2C9*2* and *CYP2C9*3* variants encode enzymes with decreased or nearly entirely neutralized function, respectively, decreasing warfarin metabolism.[1,4] The *CYP2C9*2* variant reduces the metabolism of warfarin by 30% to 50%, whereas the *CYP2C9*3* variant reduces the metabolism of the drug by 90%.[1,4] The decreased metabolism caused by these genetic variants leads to a longer half-life and a reduced rate of clearance for warfarin.[1,4] Response to warfarin has also been found to be affected by a single SNP (rs2108622) in the *CYP4F2* gene, which alters protein coding.[7]

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In 2007, the FDA modified the drug label for warfarin to include these findings, stating that *VKORC1 and CYP2C9* genotypes might be useful in determining the optimal initial dose of warfarin.[7] In 2010, the warfarin label was further updated to include a table with dosage range recommendations for patients with different combinations of *CYP2C9* and *VKORC1* genotypes.[5,7] Several warfarin dosing algorithms that incorporate both genetic and nongenetic parameters have also been developed.[5,7] A study published in 2012 reported that using patient genotype data for warfarin dosing reduced the risk of hospitalization by nearly one-third.[4]

Clopidogrel is an inactive prodrug, which is activated *in vivo* by several CYP450 enzymes, some of which are encoded by *CYP2C19*.[4] Variants in *CYP2C19* can reduce enzymatic function, lowering conversion of the clopidogrel prodrug to its active form and thus reducing efficacy.[4] This effect was originally described in two studies: the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38, and a French registry study of patients with acute myocardial infarction (MI).[4] TRITON–TIMI 38 also found that *ABCB1* and *CYP2C19* variants were significant independent predictors of cardiovascular (CV) death, MI, and stroke.[4] However, these effects were not observed in two more recent studies: Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE).[4]

Nonetheless, most investigators have concluded that the *CYP2C19* genotype influences platelet response to clopidogrel in the setting of percutaneous coronary intervention.[4] However, sufficient consensus recommending routine genetic testing in clinical practice has not emerged.[4] In 2010, the FDA added a boxed warning to the clopidogrel product information, describing patients with the *CYP2C19* polymorphism as being at higher risk of experiencing reduced efficacy with clopidogrel treatment.[1,4]

Statins, which are among the top 10 drugs prescribed in the U.S., are relatively safe, with the most common side effect being dose-dependent skeletal muscle toxicity.[7] This toxicity ranges in severity from incipient myopathy, to myopathy, to rhabdomyolysis, which is life-threatening but rare (1 in 100,000).[7]

The first GWAS to investigate statin-induced myopathy examined approximately 300,000 markers in 85 subjects with definite or incipient myopathy along with 90 controls, all of whom had taken a daily dose of simvastatin 80 mg as part of a clinical trial (n = 12,000).[7] In this study, genetic variants of *SLCO1B1*, a gene that encodes drug transporter proteins, were found to be significantly associated with the risk of myopathy.[1,7] This finding has since been replicated in several independent studies, including the Heart Protection Study, the Statin Response Examined by Genetic Haplotype Markers (STRENGTH) study, and a retrospective case–control study.[6] In 2011, the FDA updated the simvastatin product information, advising against initiation of the 80-mg dose and cautioning against continuation of an 80-mg dose unless the patient has been taking it without muscle problems for more than 1 year.[7]

Genetic Variants and Response to Opioid Drugs

Codeine is a prodrug that is converted to its active metabolite, morphine, by CYP450 enzymes that are encoded by the *CYP2D6* gene.[1,3] There are 80 *CYP2D6* variants.[1,3] The *CYP2D6*3*, **4*, **5*, **6*, and **7* alleles are reported to account for the majority of decreased *CYP2D6* enzyme activity, whereas the *CYP2D6*9* and *CYP2D6*10* alleles have been associated with decreased drug-metabolizing activity in intermediate metabolizers (IMs).[3] By contrast, the duplication of the *CYP2D6* gene in ultra-rapid metabolizers (UMs) is associated with higher morphine plasma concentrations and area-under-the-curve (AUC) concentrations compared with those observed in homozygous normal/extensive metabolizers (EMs).[3] One study evaluated oxycodone, which is structurally similar to codeine and is also metabolized by *CYP2D6* drug-metabolizing enzymes (DMEs).[3] This study showed that poor metabolizers (PMs) had a two-fold to 20-fold decrease, and UMs had a 1.5-fold to 6-fold increase, in analgesic effects compared with EMs.[3]

With respect to adverse effects, although UMs experience greater analgesic effects, they are also at an increased risk of toxicity.[3] In addition, although PMs might not experience the expected analgesic effects, they can still experience side effects (e.g., sedation, headaches, dizziness, and dry mouth), which may be associated with the codeine prodrug rather than its metabolites.[3] The AmpliChip CYP450 microarray (Roche/Affymetrix), which can detect 33 *CYP2D6* alleles, is the only

approved test for *CYP2D6* polymorphisms in the U.S.[3]

The FDA has revised the drug label for codeine to include information about *CYP2D6* polymorphisms.[12] However, there are currently no formal recommendations or requirements regarding genetic testing prior to initiating codeine treatment.[3]

Genetic Variants and Response to Proton Pump Inhibitors

The proton pump inhibitors (PPIs) omeprazole and esomeprazole (Prilosec and Nexium, AstraZeneca), lansoprazole (Prevacid, Takeda), and pantoprazole (Protonix, Pfizer) are metabolized primarily by enzymes encoded by *CYP2C19* and, to some extent, by *CYP3A*.[3] PPIs are unique, in that pharmacokinetic variability also affects drug pharmacodynamics.[3] For example, with omeprazole, the AUC time curve is 7-fold to 14-fold higher in PMs than in homozygous EMs.[3] Consequently, patients who are *CYP2C19* PMs have a higher intragastric pH compared with EMs.[3]

A higher intragastric pH has been shown to increase antibiotic concentrations and to improve antibiotic bioavailability and stability.[3] The various *Helicobacter pylori* cure rates that have been observed for PPIs can be explained to some extent by the different effects of *CYP2C19* genetic polymorphisms on PPI pharmacokinetics and pharmacodynamics.[3] In one study, Japanese patients with confirmed *H. pylori* infection received dual therapy with omeprazole and amoxicillin for several weeks.[3] Because of increased antibiotic concentrations and bioavailability resulting from higher intragastric pH for omeprazole PMs, *H. pylori* cure rates were observed to be 28.6%, 60%, and 100%, respectively, in homozygous EMs, heterozygous EMs, and PMs.[3] These results have been consistently observed in a majority of studies, which have concluded that the efficacy of omeprazole is influenced by the *CYP2C19* genotype.[3] However, some studies have yielded conflicting data, because they failed to identify a correlation between omeprazole treatment, *H. pylori* cure rates, and the *CYP2C19* genotype.[3]

Studies examining PPI dosing strategies based on the *CYP2C19* genotype are currently lacking.[3] This could be because such strategies may be of limited use due to the large therapeutic window, the many dual-therapy or triple-therapy regimens that are available, and the low incidence of clinically significant adverse effects for PPIs.[3] Although it has been suggested that higher PPI doses be considered when treating homozygous EMs, this recommendation has not yet been adopted in clinical practice.[3] However, an FDA-approved test is commercially available (AmpliChip CYP450) for *CYP2C19* genotyping.[3]

The FDA has revised the clinical pharmacology and drug-interaction sections in the prescribing information for some PPIs, such as esomeprazole, pantoprazole, and rabeprazole (e.g., Aciphex, Eisai/Janssen), to mention the effect of *CP2C19* polymorphisms on drug metabolism; however, no formal recommendations for genetic testing are included.[3]

Genetic Variants and Response to Psychotropic Drugs

Evidence accumulated over the previous 15 years indicates that genetic factors contribute substantially to drug treatment response in schizophrenic patients.[8] Most findings indicate that genetic polymorphisms that code for dopamine receptors and 5-hydroxytryptamine (5-HT, or serotonin) receptor neurotransmission are linked to symptom improvement.[8]

The primary mechanism of antipsychotic drugs involves antagonist action at dopamine D2 receptors in the brain.[8] Polymorphisms in the *DRD2*, *DRD3*, and *DRD4* genes coding for dopamine D2, D3, and D4, receptors, respectively, have been widely investigated with respect to symptom response.[8] The association of the D2-receptor gene with drug response has been confirmed in a systematic review; however, a link with the D3 receptor gene remains weak and inconsistent.[8] There have been no significant findings indicating an influence of SNPs in the dopamine D1 or D4 receptor genes with treatment response.[8] The dopamine transporter gene, *DAT,* has been positively associated with clozapine response but negatively with risperidone.[8]

Other genes that have been studied include *HTR1A* and *HTT*, which code for serotonin receptors and transporters.[8] The 5-HT_{2A} receptor is a major target that differentiates second-generation (atypical) antipsychotic drugs from older medications.[8] Although an SNP in the 5-HT_{1A} receptor gene was found to affect antipsychotic treatment response, a review of studies of SNPs in the 5-HT_{2A} receptor gene concluded that there is only a weak association with antipsychotic response as well as with psychosis itself.[8] A study of the indel sequence in the promoter region of the serotonin transporter *(HTT)* gene has been associated with an antipsychotic response in some but not all studies.[8] However, these findings have not been consistently replicated, so there is still little solid evidence supporting a correlation between pharmacogenetic associations and treatment response in patients with schizophrenia.[8] Therefore, the clinical utility of genetic screening in treating schizophrenia has not yet been established.[2]

The U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ) has also undertaken a systematic review of published studies to determine whether *CYP450* polymorphisms correlate with positive outcomes in adults taking selective serotonin reuptake inhibitors (SSRIs).[2] The AHRQ concluded that the data did not demonstrate a clear correlation between *CYP450* polymorphisms and SSRI drug levels, efficacy, or tolerability.[2]

Companion Diagnostic Tests

Although genetic research began in the 1950s, tests for genetic variants that influence drug response have become available only relatively recently.[9] The FDA has revised numerous drug labels to include information about pharmacogenetic biomarkers; however, genetic screening is still not required to initiate treatment with most of these drugs.[9] As evidence for gene–drug associations continues to emerge, changes in drug labels for both approved and new agents are likely to continue.[1,4]

Several companies manufacture FDA-approved pharmacogenetic screening tests. The first test of this type available for clinical use was the AmpliChip CYP450, which was introduced to the market in 2005.[10] This test identifies *CYP2D6* and *CYP2C19* variants that code for DMEs and predict whether a patient exhibits a PM, IM, EM, or UM phenotype.[10] This information helps to characterize how an individual will metabolize approximately 25% of prescribed drugs.[10] Another available test is the Affymetrix DMET (DMEs and transporters) chip.[10] This product evaluates polymorphisms in *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2D6*, and *CYP3A4*, *A5,* and *A7* genes.[10]

The PHARMAChip, made by Progenika Biopharma SA, is even more versatile; it enables identification of 85 of the most relevant pharmacogenetic polymorphisms with a sensitivity and specificity greater than 99.9%.[10] The PHARMAChip detects polymorphisms in CYP450 enzymes and in genes that code for drug receptors, transporters, and other targets.[10] The test also identifies whether a patient is likely to exhibit a PM, IM, EM, or UM phenotype, based on identified genetic variants, thereby enabling the determination of the type and dose of drugs that might best be used to treat the patient.[10] In 2013, two new companion diagnostic devices were approved for therapies used in non–small-cell lung cancer: the Therascreen Kit (Boehringer Ingelheim/Qiagen) for use with afatinib (Gilotrif) and the Cobas EGFR Mutation Test (Roche) for use with erlotinib.

The FDA has revised many drug labels to include information about pharmacogenetic biomarkers, but genetic screening is still not required to initiate treatment.

Companion tests are also now being used in clinical trials for drugs that are in development.[5] In July 2011, the FDA published draft guidelines requiring companion diagnostic tests to be approved simultaneously with their accompanying therapies if they are necessary for the safe and effective use of a medication.[5] The FDA approved the clinical trial design for bucindolol, a beta-blocker and mild vasodilator, in a genotype-defined population with heart failure.[4] This trial highlights the value of pharmacogenetic information for pharmaceutical companies, because drugs that don't achieve clinical endpoints required for FDA approval in the general population may successfully do so in genotype-defined subpopulations.[4]

In 2003, the FDA also initiated a voluntary data exchange program through which companies could choose to submit genomic data with their New Drug Applications (NDAs), which many drug companies now do.[1]

Despite these advances, surveys have shown that although 30% to 50% of drugs currently in development have an accompanying biomarker program, only 10% of them are expected to launch with a companion diagnostic test in the next 5 to 10 years.[5] Nonetheless, the growing frequency with which companion diagnostic tests accompany new agents is expected to encourage the clinical utilization of pharmacogenetic testing in an increasing number of therapeutic areas.[1]

Conclusion

Pharmacogenomic studies conducted in recent decades have provided an overwhelming amount of evidence regarding the influence of inter-individual genetic variations on drug response.[5] As genotyping technology becomes more advanced, cost-effective, and widely accessible, data from future studies will undoubtedly reveal many more important gene–drug associations.[8] Once the clinical utility of predictive pharmacogenetic testing becomes more widely established, genotyping is expected to be an indispensible tool in predicting and improving drug response, with the ultimate goal of personalizing patient drug treatment to provide better therapeutic outcomes.[8]

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