Genetic Factors in Drug Metabolism

DONNA J. BELLE, PhD, RPh, and HARLEEN SINGH, PharmD, *Oregon State University College of Pharmacy, Portland Campus at Oregon Health & Science University, Portland, Oregon*

Patients vary widely in their response to drugs. Having an understanding of the pharmacokinetic and pharmacodynamic properties of various medications is important when assessing ethnic differences in drug response. Genetic factors can account for 20 to 95 percent of patient variability. Genetic polymorphisms for many drug-metabolizing enzymes and drug targets (e.g., receptors) have been identified. Although currently limited to a few pathways, pharmacogenetic testing may enable physicians to understand why patients react differently to various drugs and to make better decisions about therapy. Ultimately, this understanding may shift the medical paradigm to highly individualized therapeutic regimens. ***(Am Fam Physician.*** **2008;77(11):1553-1560.** **)**

Although patient response to drugs varies widely and the reasons for this are diverse and complex, experts estimate that genetic factors account for 20 to 95 percent of patient variability in response to individual drugs.[1] Genetic influences on drug metabolism interact with other intrinsic (i.e., physiologic) and extrinsic (i.e., cultural, behavioral, and environmental) characteristics of a person to determine the outcome from treatment with any pharmacologic agent *(Table 1)*.[2]

Although still in its infancy, the field of pharmacogenetics and pharmacogenomics already provides useful clinical information to enhance patient care and offers a growing potential to individualize drug therapy and improve clinical outcomes. This article reviews the leading areas in which genetic variations currently affect treatment and indicates a need for physicians to monitor this topic as genomic-based treatment guidelines become available.

Definitions

The study of genetic variations in drug response is called pharmacogenetics when studying an individual gene, or pharmacogenomics when studying all genes. A person's genotype is his or her genetic makeup. The term can pertain to all genes or to a specific gene. The phenotype is a person's outward physical appearance or function resulting from the interaction between the genotype and the environment. Genetic polymorphisms are naturally occurring variants in gene structure that occur in more than 1 percent of the population. Polymorphisms may influence a drug's action by changing its pharmacokinetics or its pharmacodynamics.

Pharmacokinetics

Pharmacokinetics is the study of the rate and extent of drug absorption, distribution, metabolism, and excretion. These processes determine the fate of a drug in the body. A combination of metabolism and excretion constitutes drug elimination from the body.

The main routes of drug elimination are metabolism (often in the liver) and renal excretion. Genetic polymorphisms have been identified for many drug-metabolizing enzymes, including the cytochrome P450 *(CYP450)* enzymes. This gives rise to distinct population phenotypes of persons who have metabolism capabilities ranging from extremely poor to extremely fast. The large range of incidence of common CYP polymorphisms in selected population groups is illustrated in *Table 2*.[3-9] Some potential clinical consequences of these polymorphisms are listed in *Table 3*.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Physicians should consider the potential for genetic factors (intrinsic and extrinsic) to influence drug response.	C	2
When a clear genotype-response relationship has been identified and commercial testing is available, pharmacogenetic testing is preferable to the use of ethnic or race categories to individualize therapy.	C	10-12, 54, 55

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see http://www.aafp.orp/afpsort.xml.

Cytochrome P450 2C9 *(CYP2C9)*

The *CYP2C9* enzyme is involved in the metabolism of many common drugs such as glipizide (Glucotrol), tolbutamide (Orinase; brand not available in United States), losartan (Cozaar), phenytoin (Dilantin), and warfarin (Coumadin). The phenotypes *CYP2C9*2* and *CYP2C9*3* are the two most common variations and are associated with reduced enzymatic activity. *CYP2C9* is the principal enzyme responsible for the metabolism of *S*-warfarin. Persons who are *CYP2C9* poor metabolizers have reduced *S*-warfarin clearance. Clinical studies have shown that these persons require lower dosages of warfarin and are at an increased risk of excessive anticoagulation.[10,11]

Table 1. Factors Influencing Drug Response

Intrinsic		**Extrinsic**
Genetic	Physiologic	Alcohol
Absorption, distribution, metabolism, excretion	Absorption, distribution, metabolism, excretion	Climate
Body weight	Age	Culture
Genetic conditions	Alcohol	Educational status
Genetic polymorphism of drug-metabolizing enzymes	Body weight	Language
Height	Cardiovascular function	Socioeconomic factors
Race	Diet	Definition/diagnostics
Receptor sensitivity	Diseases/conditions	Diet
Sex	Height	Diseases/conditions
	Kidney function	Drug adherence
	Liver function	Medical practices
	Receptor sensitivity	Pollution
	Smoking	Smoking
	Stress	Stress
		Sunlight
		Therapeutic approach

Adapted from the U.S. Food and Drug Administration, U.S. Dept. of Health and Human Services. International Conference on Harmonisation: guidance on ethnic factors in the acceptability of foreign clinical data; availability. Federal Register 1998;63(111):31790-31796. http://www.fda.gov/cder/guidance/2293fnl.pdf. Accessed October 17, 2007.

Cytochrome P450 2C19 *(CYP2C19)*

The *CYP2C19* enzyme metabolizes many drugs, including proton pump inhibitors, citalopram (Celexa), diazepam (Valium), and imipramine (Tofranil). More than 16 variations of *CYP2C19*, associated with deficient, reduced, normal, or increased activity, have been identified. Genotyping for *CYP2C19*2* and *CYP2C19*3* identifies most *CYP2C19* poor metabolizers. The *CYP2C19*17* variant is associated with ultrarapid metabolizers and seems relatively common in Swedes (18 percent), Ethiopians (18 percent), and Chinese (4 percent).[12] The proton pump inhibitor omeprazole (Prilosec) is primarily metabolized by *CYP2C19* to its inactive metabolite, 5-hydroxyomeprazole. Persons who are *CYP2C19* poor metabolizers can have fivefold higher blood concentrations of omeprazole and experience superior acid suppression and higher cure rates than the rest of the population. Conversely, blood concentrations of omeprazole are predicted to be 40 percent lower in ultrarapid metabolizers than in the rest of the population, thus putting persons with the *CYP2C19* ultrarapid metabolizers phenotype at risk of therapeutic failure.[12]

Cytochrome P450 2D6 *(CYP2D6)*

The enzyme *CYP2D6* is involved in the metabolism of an estimated 25 percent of all drugs. More than 75 allelic variants have been identified, with enzyme activities ranging from deficient to ultrarapid. The most common variants associated with poor metabolizer phenotype are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6* in whites and *CYP2D6*17* in blacks. Codeine is metabolized by *CYP2D6* to its active metabolite, morphine. Clinical studies have shown that *CYP2D6* poor metabolizers have poor analgesic response as a result of the reduced conversion of codeine to morphine. Conversely, *CYP2D6* ultrarapid metabolizers quickly convert codeine to morphine and have enhanced analgesic response.[13]

The activity of drug-metabolizing enzymes may be induced or inhibited by many other intrinsic and extrinsic factors, including comorbid conditions, use of other medications, smoking, alcohol intake, and dietary factors.

Pharmacodynamics

Pharmacodynamics is the study of the pharmacologic effect resulting from the interaction between the drug and the biologic system. The relationship between drug concentration and the observed pharmacologic response depends on the drug's mechanism of action. The pharmacologic response to a drug may be mediated through a direct effect, such as binding with a specific

Table 2. Incidence of Cytochrome P450 Metabolizer Phenotypes Among Ethnic Groups

		Population frequency (%)		
Enzyme	*Metabolizer phenotype*	*Asians*	*Blacks*	*Whites*
CYP2C9	Poor	0.4[3]	0.0[4]	1.0[4]
	Intermediate	3.5[4]	13[4]	33[4]
	Ultrarapid	—	—	—
CYP2C19	Poor	18 to 23[3,5]	1.2 to 5.3[5,6]	2.0 to 5.0[3,5]
	Intermediate	30[7]	29[7,8]	18[7]
	Ultrarapid	—	—	—
CYP2D6	Poor	1.0 to 4.8[3,5,8]	1.9 to 7.3[5,6,8]	7.0 to 10[3,8]
	Intermediate	51[8]	30[9]	1.0 to 2.0[8]
	Ultrarapid	0.9 to 21[8]	4.9[8]	1.0 to 5.0[8]

NOTE: *Poor metabolizers have markedly reduced or absent enzyme activity; intermediate metabolizers have reduced enzyme activity; and ultrarapid metabolizers have high enzyme activity.*

CYP = cytochrome P450.

Information from references 3 through 9.

Table 3. Clinical Consequence of Metabolizer Phenotypes on Drug Response

Drug type	*Metabolizer phenotype*	*Effect on drug metabolism*	*Potential consequence*
Prodrug, needs metabolism to work (e.g., codeine metabolized to morphine)	Poor to intermediate	Slow	Poor drug efficacy, patient at risk of therapeutic failure
			Accumulation of prodrug, patient at increased risk of drug-induced side effects
	Ultrarapid	Fast	Good drug efficacy, rapid effect
Active drug metabolized to inactive drug (e.g., omeprazole [Prilosec] metabolized to 5-hydroxyomeprazole)	Poor to intermediate	Slow	Good drug efficacy
			Accumulation of active drug, patient at increased risk of drug-induced side effects
			Patient requires lower dosage
	Ultrarapid	Fast	Poor drug efficacy, patient at risk of therapeutic failure
			Patient requires higher dosage

NOTE: *Poor metabolizers have markedly reduced or absent enzyme activity; intermediate metabolizers have reduced enzyme activity; and ultrarapid metabolizers have high enzyme activity.*

receptor, or an indirect effect, such as inhibiting an enzyme in a protein synthesis pathway.

Pharmacogenomics in Common Conditions

CARDIOVASCULAR CONDITIONS

Hypertension is a major risk factor for cardiovascular morbidity and mortality.[14] Despite the availability of several pharmacologic treatment options for hypertension, only 34 percent of North Americans are achieving target blood pressure goals, and preventing cardiovascular complications is still a notable challenge.[15] Extrinsic (e.g., increased sodium intake, decreased calcium and potassium intake, psychosocial stressors) and intrinsic factors (e.g., low plasma renin activity, higher prevalence of expanded plasma volume, reduced sodium-potassium adenosinetriphosphatase activity, increased intracellular sodium concentrations, elevated fasting insulin levels) may explain the potentially different pathophysiology of hypertension in blacks and whites.[16] This has led to the discovery of candidate genes for hypertension *(Table 4[10,16-25])*. Polymorphism in these genes may be responsible for the high prevalence and increased severity of hypertension in black persons.[16,26-28] The enhanced effects of diuretics in blacks are likely related to many of the extrinsic and intrinsic factors listed above.[16,26]

Typically, black patients require a high dosage of angiotensin-converting enzyme (ACE) inhibitors or combined therapy with low-dose diuretics to reduce blood pressure effectively.[29] Although the risk of ACE-related angioedema is generally low, there is some evidence that it is more common

Table 4. Genetic Polymorphisms in Drug Receptor Genes Associated with Drug Response

Gene	*Drug class (drug)*	*Response*
ACE	ACE inhibitors, ARBs, statins (fluvastatin [Lescol]), and fibrates (gemfibrozil [Lopid])	Greater blood pressure reduction[17] Greater LDL cholesterol reduction, increase in HDL cholesterol with statins and fibrates
Alpha-adducin	Diuretics (hydrochlorothiazide)	Better blood pressure control with diuretics and fewer cardiovascular events[16,18]
Angiotensinogen	ACE inhibitors and ARBs (irbesartan [Avapro])	Greater reduction in blood pressure and left ventricle mass with ACE inhibitors and ARBs[19]
Apolipoprotein E	Statins (simvastatin [Zocor])	Greater mortality reduction with simvastatin[20]
Beta-fibrinogen	Statins (pravastatin [Pravachol])	Reduction in coronary atherosclerosis[21]
β_1-adrenergic receptors	Beta blockers (metoprolol [Lopressor])	Greater reduction in blood pressure
β_2-adrenergic receptors	$Beta_2$-adrenergic agonists (albuterol [Proventil])	May affect survival in heart failure Positive response to bronchodilator therapy[22]
Cholesteryl ester transfer protein	Statins (pravastatin) Fibrates (gemfibrozil)	Greater effects of pravastatin on slowing coronary atherosclerosis[23] Greater reductions in triglycerides
Leukotriene C_4 synthase	Leukotriene receptor antagonists (zafirlukast [Accolate])	Improvement in FEV_1[24]
5-lipoxygenase	Leukotriene receptor antagonists	May affect disease predisposition of asthma
Stromelysin-1	Statins (i.e., pravastatin)	Pravastatin reduced the incidence of coronary artery restenosis and repeat angioplasty[25]
Vitamin K epoxide reductase complex subunit 1	Warfarin (Coumadin)	Less variability in dose response[10]

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; FEV_1 = forced expiratory volume in one second; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Information from references 10, and 16 through 25.

in blacks.[30] Despite the differences between black persons and other ethnic groups, ACE inhibitors have proven highly effective in reducing morbidity and mortality in patients with hypertension who present with other comorbidities such as heart failure, diabetic nephropathy, and myocardial infarction.[14]

Advances in drug therapy have helped reduce mortality in many patients with heart failure, but it is unclear whether all population groups have benefited. Beta blockers and ACE inhibitors are the standard of care in patients with heart failure.[31] Therapeutic outcomes have been highly variable, possibly secondary to genetic variability in β-adrenergic receptors, the renin-angiotensin-aldosterone system, the endothelin system, and endothelial nitrogen monoxide synthase.[32] One of the most important genetic polymorphisms studied in heart failure is an insertion/deletion (I/D) polymorphism of the ACE gene. Persons who are D carriers have higher ACE activity and are at increased risk of developing cardiovascular disease.[33,34] Similarly, the response to beta blockers is highly variable in patients with heart failure.[35,36]

Recently, the African American Heart Failure Trial (A-HeFT) demonstrated that adding isosorbide dinitrate (Isochron) and hydralazine (Apresoline; brand not available in United States) to standard therapy for heart failure increases survival in black patients with advanced heart failure.[37] It has been proposed that nitric oxide deficiency can result in the progression of heart failure.[38] Patients exhibiting genetic polymorphism may have less nitric oxide and, thus, may benefit from nitric oxide–enhancing therapy. Because this study included only black patients, it lacked evidence of differences in response between white and black Americans. The gene or genes responsible for nitric oxide deficiency have not been identified in black persons. However, several biologic systems are involved in the pathogenesis of heart failure, and each is highly polymorphic. Currently, no prospective studies are investigating the simultaneous impact of multiple genetic variants on cardiovascular outcomes.

Several genes are associated with coronary heart disease (CHD). The involvement of multiple genes with potential polymorphisms makes predicting persons at risk of developing CHD highly imprecise. Examples of genes affecting CHD include the cholesteryl ester transfer protein, stromelysin-1, beta-fibrinogen, and apolipoprotein E genes. Descriptions of genetic polymorphisms associated with CHD and their response to statin therapy are summarized in *Table 4*.[10,16-25]

ASTHMA

Approximately 8 to 10 percent of the U.S. population is affected by asthma. In terms of morbidity and cost, asthma is considered a major health risk.[39] Research has focused on identifying the potential role of genetics in the pathophysiology and management of asthma.[40-43] Common drugs used to control asthma are $beta_2$ agonists (both short- and long-acting), inhaled corticosteroids, and leukotriene antagonists. Response to asthma medications is highly variable, with only 60 to 80 percent of patients deriving therapeutic benefit.[40]

Inhaled $beta_2$ agonists, such as albuterol (Proventil), are used to control acute attacks of asthma and are prescribed to be used "as needed." Several studies have shown that some patients benefit from use of short-acting $beta_2$ agonists whereas others do not.[22,44] This variation in response is partly explained by the alteration in the amino acid sequence of the protein or altered transcription of the $beta_2$ receptors. Patients with the $beta_2$ receptor arginine genotype experience poor asthma control with frequent symptoms and a decrease in scores on forced expiratory volume in one second compared with patients who have the glycine genotype.[22,45] Studies show that 17 percent of whites and 20 percent of blacks carry the arginine genotype.[46]

Leukotriene (LT) modifiers (e.g., zileuton [Zyflo], montelukast [Singulair], zafirlukast [Accolate]) block the 5-lipoxygenase (5-LO) and LTC_4 synthase pathways, preventing leukotriene-mediated bronchoconstriction.[47,48] Only a minority of patients benefit from treatment with LT receptor agonists. Polymorphism in 5-LO and LTC_4 synthase pathways has been identified *(Table 4*[10,16-25]*)*. Approximately 5 percent of patients with

asthma have the 5-LO polymorphism. Patients who had the 5-LO polymorphism showed a greater improvement in their lung function with zafirlukast therapy compared with patients who had the normal 5-LO genotype. Similarly, polymorphisms in the LTC_4 synthase gene may predispose a person to asthma. Patients with the variant LTC_4 synthase genotype have higher levels of cysteinyl leukotrienes, which have been linked with severe asthma. The use of LT modifiers in this population may be beneficial.[24,49]

Variation in the genes involved in the biologic action of inhaled corticosteroids may explain the variability to response and adverse effects to inhaled corticosteroids. Polymorphisms in corticotropin-releasing hormone receptor-1 and T-box expressed in T cells have been associated with improved response in patients with asthma.[50,51] Although these findings are promising in predicting therapeutic response to asthma medication, their usefulness in clinical practice is still under investigation.

Warfarin

Warfarin dosing can be challenging because of its narrow therapeutic index and the serious risk of bleeding with overdosage. Typically, warfarin dosing is individualized based on sex, age, vitamin K intake, drug interactions, and disease states. Dosing adjustments are made according to the desired International Normalized Ratio. Environmental and genetic factors can influence warfarin response. Several studies have focused on *CYP2C9* polymorphisms to explain patient variability with warfarin therapy. Only about 10 percent of dosage variation in warfarin can be explained by *CYP2C9* polymorphisms.

Prospective genetic testing could be beneficial for drugs for which a clear genotype-response relationship has been demonstrated.

Warfarin exerts its anticoagulant effects by inhibiting hepatic vitamin K epoxide reductase, an enzyme involved in the synthesis of various clotting factors. Polymorphisms in the vitamin K epoxide reductase complex subunit 1 *(VKORC1)* gene have been identified and are believed to contribute to the variability in warfarin responsiveness.[10] Understanding environmental and genetic factors will allow the physician to more accurately dose warfarin and improve anticoagulation control.

Limitations of the Current Literature on Pharmacogenomics

Most pharmacodynamic studies have been relatively small and the populations studied are not always well characterized. Ethnic categories (e.g., Asians, blacks, whites) include persons from widely diverse geographic and sociocultural backgrounds with varying genetic composition, and the results might not apply to all members of each ethnic population. Typically, pharmacokinetic variability is no greater than pharmacodynamic variability; however, in most studies, only selected pharmacokinetic parameters were examined.

Use of genotyping is more accurate than race or ethnic categories to identify variations in drug response.[52] Unlike other influences on drug response, genetic factors remain constant throughout life. The use of pharmacogenetic information to support drug selection and dosing is emerging. Commercial testing is available for drug-metabolizing enzymes and some pharmacodynamic targets such as *VKORC1*, stromelysin-1, and apolipoprotein E.[53,54] Prospective genetic testing would be beneficial for drugs for which a clear genotype-response relationship has been demonstrated, such as warfarin (*CYP2C9*, *VKORC1)* and proton pump inhibitors (*CYP2C19*). The U.S. Food and Drug Administration has suggested relabeling warfarin to include genetic information to guide initial dosing.[55]

The authors thank Ganesh Cherala, PhD, for reviewing the manuscript, and Nathan Thomas for his technical expertise in the preparation of the manuscript.

This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

The Authors

DONNA J. BELLE, PhD, RPh, was an assistant research professor of pharmacokinetics in the College of Pharmacy, Oregon State University, Portland, at the time she

coauthored this article. Dr. Belle received her doctorate degree from the School of Pharmacy at West Virginia University, Morgantown, and completed a postdoctoral research fellowship in the Department of Drug Disposition at Eli Lilly and Company, Indianapolis, Ind.

HARLEEN SINGH, PharmD, is an assistant professor of pharmacy in the Department of Pharmacy Practice, College of Pharmacy, Oregon State University. Dr. Singh received her doctor of pharmacy degree from Ohio State University College of Pharmacy, Columbus, where she also completed a residency in adult medicine.

Address correspondence to Harleen Singh, PharmD, Oregon State University College of Pharmacy, 3303 SW Bond Ave., CH12C, Portland, OR 97239 (e-mail: singhh@ohsu.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. *Pharmacogenetics*. 1998;8(4):283-289.
2. U.S. Food and Drug Administration, U.S. Dept. of Health and Human Services. International Conference on Harmonisation: guidance on ethnic factors in the acceptability of foreign clinical data; availability. Federal Register 1998;63(111):31790-31796. http://www.fda.gov/cder/guidance/2293fnl.pdf. Accessed October 17, 2007.
3. Mizutani T. PM frequencies of major CYPs in Asians and Caucasians. *Drug Metab Rev.* 2003;35(2-3):99-106.
4. Kirchheiner J, Brockmöller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin Pharmacol Ther.* 2005;77(1):1-16.
5. Ozawa S, Soyama A, Saeki M, et al. Ethnic differences in genetic polymorphisms of *CYP2D6, CYP2C19,* CYP3As and MDR1/ABCB1. *Drug Metab Pharmacokinet*. 2004; 19(2):83-95.
6. Dandara C, Masimirembwa CM, Magimba A, et al. Genetic polymorphism of *CYP2D6* and *CYP2C19* in east- and southern African populations including psychiatric patients. *Eur J Clin Pharmacol*. 2001;57(1):11-17.
7. Luo HR, Poland RE, Lin KM, Wan YJ. Genetic polymorphism of cytochrome P450 2C19 in Mexican Americans: a cross-ethnic comparative study. *Clin Pharmacol Ther.* 2006;80(1):33-40.
8. Bernard S, Neville KA, Nguyen AT, Flockhart DA. Interethnic differences in genetic polymorphisms of *CYP2D6* in the U.S. population: clinical implications. *Oncologist*. 2006;11(2):126-135.
9. Gaedigk A, Bradford LD, Marcucci KA, Leeder JS. Unique *CYP2D6* activity distribution and genotype-phenotype discordance in black Americans. *Clin Pharmacol Ther.* 2002;72(1):76-89.
10. Aquilante CL, Langaee TY, Lopez LM, et al. Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. *Clin Pharmacol Ther.* 2006;79(4):291-302.
11. Higashi MK, Veenstra DL, Kondo LM, et al. Association between *CYP2C9* genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA*. 2002;287(13):1690-1698.
12. Sim SC, Risinger C, Dahl ML, et al. A common novel *CYP2C19* gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther.* 2006;79(1):103-113.
13. de Leon J, Dinsmore L, Wedlund P. Adverse drug reactions to oxycodone and hydrocodone in *CYP2D6* ultrarapid metabolizers. *J Clin Psychopharmacol*. 2003; 23(4):420-421.
14. Chobanian AV, Bakris GL, Black HR, et al.; for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA*. 2003;290(2):197]. *JAMA*. 2003;289(19):2560-2572.
15. Johnson JA, Turner ST. Hypertension pharmacogenomics: current status and future directions. *Curr Opin Mol Ther.* 2005;7(3):218-225.
16. Richardson AD, Piepho RW. Effect of race on hypertension and antihypertensive therapy. *Int J Clin Pharmacol Ther.* 2000;38(2):75-79.
17. Hingorani AD, Jia H, Stevens PA, Hopper R, Dickerson JE, Brown MJ. Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. *J Hypertens*. 1995;13(12 pt 2):1602-1609.
18. Psaty BM, Smith NL, Heckbert SR, et al. Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. *JAMA*. 2002;287(13):1680-1689.
19. Kurland L, Melhus H, Karlsson J, et al. Aldosterone synthase (CYP11B2) –344 C/T polymorphism is related to antihypertensive response: result from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA) trial. *Am J Hypertens*. 2002;15(5):389-393.
20. Gerdes LU, Gerdes C, Kervinen K, et al. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction: a substudy of the Scandinavian simvastatin survival study. *Circulation*. 2000;101(12):1366-1371.
21. de Maat MP, Kastelein JJ, Jukema JW, et al. –455G/A polymorphism of the beta-fibrinogen gene is associated with the progression of coronary atherosclerosis in symptomatic men: proposed role for an acute-phase reaction pattern of fibrinogen. REGRESS group. *Arterioscler Thromb Vasc Biol*. 1998;18(2):265-271.
22. Israel E, Drazen JM, Liggett SB, et al.; for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Effect of polymorphism of the beta(2)-adrenergic receptor on response to regular use of albuterol in asthma. *Int Arch Allergy Immunol*. 2001;124(1-3):183-186.
23. Brousseau ME, O'Connor JJ Jr, Ordovas JM, et al. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol levels and lower risk of coronary heart disease end points in men with HDL deficiency: Veterans Affairs HDL Cholesterol Intervention Trial. *Arterioscler Thromb Vasc Biol*. 2002;22(7):1148-1154.

24. Cowburn AS, Sladek K, Soja J, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest*. 1998;101(4):834-846.
25. de Maat MP, Jukema JW, Ye S, et al. Effect of the stromelysin-1 promoter on efficacy of pravastatin in coronary atherosclerosis and restenosis. *Am J Cardiol*. 1999;83(6):852-856.
26. Gibbs CR, Beevers DG, Lip GY. The management of hypertensive disease in black patients. *QJM*. 1999;92(4):187-192.
27. Koopmans RP, Insel PA, Michel MC. Pharmacogenetics of hypertension treatment: a structured review. *Pharmacogenetics*. 2003;13(12):705-713.
28. Trotta R, Donati MB, Iacoviello L. Trends in pharmacogenomics of drugs acting on hypertension. *Pharmacol Res*. 2004;49(4):351-356.
29. Amudha K, Wong LP, Choy AM, Lang CC. Ethnicity and drug therapy for hypertension. *Curr Pharm Des*. 2003;9(21):1691-1701.
30. Douglas JG, Bakris GL, Epstein M, et al., for the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med*. 2003; 163(5):525-541.
31. Hebert PR, Foody JM, Hennekens CH. The renin-angiotensin system: the role of inhibitors, blockers, and genetic polymorphisms in the treatment and prevention of heart failure. *Curr Vasc Pharmacol*. 2003;1(1):33-39.
32. Cascorbi I, Paul M, Kroemer HK. Pharmacogenomics of heart failure–focus on drug disposition and action. *Cardiovasc Res*. 2004;64(1):32-39.
33. Kohno M, Yokokawa K, Minami M, et al. Association between angiotensin-converting enzyme gene polymorphisms and regression of left ventricular hypertrophy in patients treated with angiotensin-converting enzyme inhibitors. *Am J Med*. 1999;106(5):544-549.
34. McNamara DM, Holubkov R, Postava L, et al. Pharmacogenetic interactions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. *J Am Coll Cardiol*. 2004;44(10): 2019-2026.
35. Forleo C, Resta N, Sorrentino S, et al. Association of beta-adrenergic receptor polymorphisms and progression to heart failure in patients with idiopathic dilated cardiomyopathy. *Am J Med*. 2004;117(7):451-458.
36. Terra SG, Pauly DF, Lee CR, et al. beta-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. *Clin Pharmacol Ther*. 2005;77(3):127-137.
37. Taylor AL, Ziesche S, Yancy C, et al.; for the African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure [published correction appears in *N Engl J Med*. 2005;352(12):1276]. *N Engl J Med*. 2004; 351(20):2049-2057.
38. Münzel T, Harrison DG. Increased superoxide in heart failure: a biochemical baroreflex gone awry. *Circulation*. 1999;100(3):216-218.
39. Busse W, Banks-Schlegel S, Noel P, Ortega H, Taggart V, Elias J, for the NHLBI Working Group. Future research directions in asthma: an NHLBI Working Group report. *Am J Respir Crit Care Med*. 2004;170(6):683-690.
40. Pignatti PF. Trends in pharmacogenomics of drugs used in the treatment of asthma. *Pharmacol Res*. 2004; 49(4):343-349.
41. Wallace AM, Sandford AJ. Therapeutic response to asthma medications: genotype predictors. *Treat Respir Med*. 2004;3(3):161-171.
42. Tantisira KG, Weiss ST. The pharmacogenetics of asthma: an update. *Curr Opin Mol Ther*. 2005;7(3):209-217.
43. Sayers I, Hall IP. Pharmacogenetic approaches in the treatment of asthma. *Curr Allergy Asthma Rep*. 2005; 5(2):101-108.
44. Liggett SB, Shah SD, Cryer PE. Characterization of beta-adrenergic receptors of human skeletal muscle obtained by needle biopsy. *Am J Physiol*. 1988;254(6 pt 1): E795-E798.
45. Tan S, Hall IP, Dewar J, Dow E, Lipworth B. Association between beta 2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics. *Lancet*. 1997; 350(9083):995-999.
46. Wechsler ME, Israel E. How pharmacogenomics will play a role in the management of asthma. *Am J Respir Crit Care Med*. 2005;172(1):12-18.
47. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway [published corrections appear in *N Engl J Med*. 1999;340(8):663 and *N Engl J Med*. 1999;341(21):1632]. *N Engl J Med*. 1999;340(3):197-206.
48. Sampson AP. Leukotriene genetics and the efficacy of leukotriene-receptor antagonists. *RT J Respir Care Practitioners*. 2004;17:30-32.
49. Asano K, Shiomi T, Hasegawa N, et al. Leukotriene C4 synthase gene A(−444)C polymorphism and clinical response to a CYS-LT(1) antagonist, pranlukast, in Japanese patients with moderate asthma. *Pharmacogenetics*. 2002;12(7):565-570.
50. Tantisira KG, Hwang ES, Raby BA, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proc Natl Acad Sci U S A*. 2004;101(52):18099-18104.
51. Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. *Hum Mol Genet*. 2004;13(13):1353-1359.
52. Wilson JF, Weale ME, Smith AC, et al. Population genetic structure of variable drug response. *Nat Genet*. 2001; 29(3):265-269.
53. Pharmacogentics: personalizing medicine today! http://www.healthanddna.com/professional/pharmacogenetics.html. Accessed October 17, 2007.
54. Molecular Diagnostics Laboratories. http://www.mdl-labs.com/testing/. Accessed February 14, 2008.
55. U.S. Food and Drug Administration Pharmaceutical Science Advisory Committee. November 14-15, 2005. http://www.fda.gov/ohrms/dockets/ac/cder05.html#PharmScience. Accessed October 17, 2007.