

Review Article

PHARMACOGENOMICS AND PERSONALIZED MANAGEMENT OF HYPERTENSION

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ABSTRACT

Personalized medicine is a long-term vision, a formidable challenge, and will require varied approaches to achieve success. Concept of right medicine to the right individual at the right dose and at the right time is personalized medicine. Using the approach of personalized medicine and Knowledge of genetic factors that predict antihypertensive drug response may eventually enable clinicians to choose the most effective drug for each individual patient based on his or her genetic profile. This tailored therapy may help patients achieve better blood pressure control and may help to reduce the costs and adverse effects of antihypertensive therapy.

Keywords: GWAS: genome-wide association study, SNP: single nucleotide polymorphisms, EMA: European medical agency.

INTRODUCTION

Pharmacogenetics deals with heredity and responses to drugs. It is a branch of science that attempts to explain variability of drug responses, and to search for the genetic basis of such variations or differences. Early on, pharmacogenetics research examined differences between individual subjects, but as it developed, it also became concerned with genetic differences between populations. A report from the laboratory of Dr. Robert Smith in London became a milestone in pharmacogenetics. He described the deficient metabolism of debrisoquine, a deficiency he had personally experienced as a life threatening drop of blood pressure after taking the drug [1, 2].

It was reported in 1975 in a thesis a metabolic deficiency of sparteine metabolism; due to deficiency of the P450 cytochrome (CYP2D6) enzyme affects the metabolism of more than 40 drugs; where ever More than 70 different variants of CYP2D6 were known at that time and many were found completely without any trace of activity [3]. On the other hand, gene duplication or multiplication in some subject's cause's extremely high CYP2D6 activity [4]. It is not surprising that most initial discoveries in pharmacogenetics pertained to drug metabolizing enzymes as the measurements of drugs and drug metabolites required chemical analytical methods of more or less traditional nature. Investigation of receptor variation usually requires knowledge of the receptor's DNA sequence [5]. Factors that cause variations in drug response are multifold and complex, some of which involve fundamental aspects of human biology, because a drug response directly affects well being and survival. It was reveled from clinical observations in the late 1950s that Genetic variation in humans was recognized as an important determinant of individual variability of drug response [6-8]. The human genome sequence provides information of human evolution that varies among populations and individuals. Sequence variations in drug target proteins, drug-metabolizing enzymes, and drug transporters can alter drug efficacy, drug side effects, or both to cause variable drug responses in individual patients [9-16]. In the recent years, significant technological advancements have been achieved in the field of genomics. This has resulted in possibilities to investigate the contribution of the genome to human health and disease and possibilities of the personalized medicine. Within the field of genomics, it is important to distinguish between genomics for estimating disease risk and prognosis and pharmacogenomics. The EMA defines pharmacogenomics as "the investigation of variations in DNA and RNA characteristics as related to drug response [17]. The ultimate aim of pharmacogenomics is the identification of genetic variants that underlie inter-individual variation in drug

response [18]. DNA sequencing and genotyping technologies, has begun to enhance our understanding of human diversity in pharmacologic traits [19]. Such as the genome-wide association study (GWAS) approach, have facilitated the discovery of genetic variation with considerable clinical relevance [20].

Pharmacogenomics and biomarkers

A great deal of attention is being directed to developing a better understanding of heterogeneity in disease, in patients and in drug response profiles. The identification and use of various biomarkers to characterize disease and patient heterogeneity, as well as heterogeneity of drug response is needed. Biomarkers include laboratory-based markers such as based on changes in gene and protein expression and Non-laboratory-based biomarkers such as imaging-based approaches (MRI) [21].

Over the past few years, single nucleotide polymorphisms (SNPs) have been identified as the best marker of genetic variation. SNPs have been identified because they are widely distributed throughout the genome, they involve mostly substitutions, they have low rates of mutation, and their measurement is amenable using high-throughput genotyping methods. SNPs in drug metabolizing enzymes have long been informative and useful in guiding therapeutic decisions regarding dose selections. Important genetic variations are in DNA (SNPs) in regions of genomic or nongenomic structure at the germ line level, the somatic level (i.e., cancer), or both. Genotypes or haplotypes within specific candidate genes may be informative. SNPs may also be found outside gene regions. Genome wide SNP maps, including SNPs inside and outside of gene regions, may also prove to be valuable in delineating drug response patterns especially when the map includes more than 500, 000 SNPs. This will provide an opportunity to explore the utility of linkage disequilibrium (LD) at distances of 5-10 kb or less [22, 23].

Personalized medicine

Personalized medicine is a long-term vision, a formidable challenge, and will require varied approaches to achieve success. Discoveries from emerging information and knowledge from genomic, genetic, and proteomic sciences will contribute significantly to achieving personalized medicine. This may apply both to medicines already approved, as well as to drug candidates under evaluation in clinical trials during the drug development process. Concept of right medicine, right dose at the right time and to the right individual is personalized medicine. Pharma cogenomics seeks to identify genomic, genetic, and proteomic data

and to develop associations between these data and drug response patterns. This is intended to explain inter patient variability in

drug response, and to predict likely response in individuals receiving a particular medicine.

Table1: Showing variations in drug response

Disease	Drug class	Poor /Non responders	Reference
Asthma	Beta-2 adrenergic agonist, 5-LO, LTD4	40-75	[24, 25]
Cancer (breast, lung, brain)	Various	70-100	[26, 27, 28]
Depression	SSRIs, tricyclics, MAOs	20-40	[29, 30, 31, 32]
Diabetes	Sulfonylureas, biguanides, glitazones	50-75	[33, 34]
Duodenal ulcer	H2 antagonists, proton pump inhibitors	20-70	[35]

In the early 1980s, clinical differences in response to the blood pressure lowering effects of β blockers and, to a lesser extent, diuretics were noted between ethnic groups. The most convincing evidence at that time came from a Veterans Affairs (VA) Cooperative Trial 1982 [36], which, along with other smaller studies, suggested that whites (those of European ancestry) had a better antihypertensive response to β blockers than blacks (those of African ancestry), whereas blacks had a slight better response to diuretics than whites. Shortly after the first angiotensin converting enzyme (ACE) inhibitor was approved in the mid-1980s, it was also recognized that whites responded more favorably to ACE inhibitors than did blacks so present review will summarize the examples for therapy of hypertension and use of Personalized medicine.

It is beyond doubt that pharmacogenomics promotes the development of targeted therapies, as was demonstrated by the approval earlier this year of the drug ivacaftor by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of a subset of cystic fibrosis patients. Ivacaftor is approved only for cystic fibrosis patients bearing the specific G551D genetic variant in the cystic fibrosis trans membrane regulator (*CFTR*) gene, which encodes a protein that regulates chloride and water transport in the body and is defective in the disease. Ivacaftor targets the CFTR protein, increases its activity, and consequently improves lung function [37].

Several important applications of pharmacogenomics are already being used in clinical practice and some of them have been approved by the FDA (for example, cetuximab/panitumumab and *KRAS*; vemurafenib and *BRAF*; warfarin and *CYP2C9/VKORC1*; abacavir and *HLA-B*5701*; carbamazepin and *HLA-B*1502*; thiopurines and *TPMT* [38])

Pharmacogenomics of hypertension

Antihypertensive pharmacogenetics research has the potential to discover genetic contributors to variability in antihypertensive response, and tailoring therapy based on an individual's genetic make-up and has the potential to diminish cardiovascular disease (CVD) outcomes among treated hypertensive. Despite the repeated observation in multiple populations that approximately 50% of the variation in blood pressure is explained by genetic factors, individual genes that account for a large proportion of the variation in blood pressure in the population have yet to be identified. Part of the complexity of the blood pressure phenotype is that alleles at many loci in a number of pathways as well as many environmental factors contribute to its expression. Evidence suggests that the between-person variation in response to blood pressure-lowering drugs is also partially under genetic control [39]. Since the blood pressure response to drugs follows a normal distribution, multiple genetic factors are likely to contribute to treatment response. Indeed, genetic variations observed in blood pressure-regulating drug receptors (e.g., β_1 adrenergic receptors) and receptor response pathways (G-protein β_3 subunit, renin-angiotensin-aldosterone system) have been associated with differential responses to blood pressure-lowering treatment [40-42].

It is common clinical experience that individual patients vary in their response to different types of anti-hypertensive drugs. In one study conducted by the Veterans Affairs Cooperative Study Group on Antihypertensive Agents, men with diastolic blood pressures of 95 ± 109 mmHg were randomly assigned to treatment with one of six

antihypertensive agents (hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem or prazosin), each having a different mechanism of action. After dosages were titrated upward to achieve maximal effects, the percentage of patients in whom diastolic blood pressure was lowered to 90 mmHg was similar among drugs and was only slightly greater than 50% for most drugs [43, 44] African Americans are reported to be more responsive to diuretics and calcium channel blockers and less responsive to α -blockers and angiotensin converting enzyme inhibitors than their Caucasian counterparts [43, 45-47]. Neither gender, nor age, nor measures of body size has been found to predict response [48-50, 46, 51]. While some reported measurement of plasma renin activity, indexed to sodium intake, to aid selection of antihypertensive drug therapy [52-54,] other investigators find this approach no more predictive than simply determined characteristics of race and age [55, 56].

One more example shows ethnic difference in the response of antihypertensive medication is the much poorer response of black subjects to angiotensin-converting enzyme (ACE)inhibitors compared with that of Caucasians [57] in their study of 56 white patients (aged 22-51 years) from the East Anglia region of the U. K. with previously untreated essential hypertension, who were rotated through the four main classes of anti-hypertensive drugs (diuretics, β -blockers, calcium antagonists and ACE inhibitors). Only 22 out of 56 (39%) individuals achieved the target blood pressure with their first drug but this increased to 41 out of 56 (73%) when the best response was considered, supporting the concept of individual variability in anti-hypertensive response. It is clear that ethnicity does not sufficiently separate those for whom a given therapy will be effective versus ineffective. The potential promise of pharmacogenetics is that it may present a more effective way of identifying responders and non responders, allowing clinicians to begin to move away from use of ethnicity as a method for selecting therapy. The reasons for the inter-individual variation in responses to anti-hypertensive agents are poorly understood. Genetically determined variation in drug metabolism that could impact on bioavailability may be one of the less important factor which has been documented for some anti-hypertensive agents. Although single gene polymorphisms with large effects on drug metabolism have been at the forefront of pharmacogenetics investigation since its beginning several factors diminish their relevance to contemporary clinical practice [58].

Most of the variation is probably a direct consequence of the heterogeneity of mechanisms underlying 'essential' hypertension. Since genetic factors make a significant contribution to this heterogeneity, a hope that is often expressed is that elucidation of the nature of the inherited factors and a better molecular characterization of hypertension may allow a more informed therapeutic choice to be made. Several genes have now, at least tentatively, been linked and/or associated with essential hypertension [59] such as polymorphisms in the angiotensinogen gene, adducin gene, β adreno receptor gene etc. These studies have advanced our understanding of the potential role of genetics in variable response to antihypertensive drugs. Pharmacogenomic studies have now been published on all five major antihypertensive drug classes. There are some examples where the literature seems quite promising as it relates to hypertension pharmacogenomics.

Consequently, there has been major interest in identifying genes that influence the pharmacodynamic determinants of blood pressure

response. Some progress is being made using candidate gene and genome scanning approaches. With advances in high throughput and rapid genotyping of large number of genetic polymorphism, pharmacogenetic studies that examine the influence of genetic variation in the response to antihypertensive medication are now possible. Many studies now published and examined the association between blood pressure response and specific gene polymorphism. Angiotension – converting enzyme (ACE) inhibitors and β blockers have been most frequently studied antihypertensive drugs (17 studies each) followed by angiotensin 2 blockers (10 studies), Diuretic (10 studies), adrenergic alpha agonist calcium channel blocker (one study each) [60].

Table 2: Summary of clinical investigation done on the effect of β 1-Adrenergic Receptors genetic polymorphisms

Healthy volunteers		Outcomes	β -Blocker Response	Refrence
β -Blocker	N			
Atenolol	34	BP response to a single dose	Arg>Gly	[65]
Metoprolol	16	Reduction in exercise-induced HR and BP increase	Arg>Gly	[66]
Bisoprolol	18	Reduction in dobutamine-induced HR	Arg>Gly	[67]
Hypertensive patients				
Metoprolol	40	24-hr and day-time diastolic blood pressure	Arg>Gly	[61]
Metoprolol	61	BP response	Arg>Gly	[42]
Atenolol	147	BP and HR response	Arg = Gly	[62]
Atenolol	101	BP and HR response	Arg = Gly	[63]
Atenolol	270	BP response	Arg = Gly	[64]

β -adrenergic receptors gene

The pharmacological effects of β -blockers derive from their ability to antagonize the β adrenergic receptor. Thus, the genes for these receptors have been a primary focus in β -blocker pharmacogenetic studies. In the cardiovascular system, there are two β -adrenergic receptors that β -blockers can antagonize: β 1-adrenergic receptor and β 2-adrenergic receptor, both of which are members of the G-protein coupled receptors super family.

β -1 adrenergic receptor

The β 1-adrenergic receptor gene (ADRB1), consisting of 2,860 bp, is located in chromosome 10q24-26. It encodes a 51.3 kDa protein, with 477 amino acid residues. β 1-adrenergic receptor are primarily found in the heart, controlling contractility, and heart rate. β 1-adrenergic receptor are also expressed in kidney, vasculature, and adipose tissues. There are 13 validated SNPs in the ADRB1, which have been reported to the National Center for Biotechnology Information Single Nucleotide Polymorphism database (dbSNP).

An additional six validated SNPs located near the ADRB1 gene region are also found in dbSNP. Of these SNPs, two polymorphisms have been extensively studied both *in vitro* and *in vivo*: Ser49Gly (nt 34552562 A→G on NT_030059 , rs1801252) and Arg389Gly (nt 34553582 C→G

on NT_030059, rs1801253). The Ser49Gly polymorphism is located in the N-terminus and the Arg389Gly polymorphism is located in a putative G-protein binding. One study carried out by Rochais *et al.* 2007 using fluorescent resonance energy transfer (FRET)-based approach compared β 1-adrenergic receptor binding affinity of the three β -blockers (bisoprolol, metoprolol, and carvedilol) between Arg389 and Gly389 receptors and reported Gly-389-b1-AR showed a comparable degree of inhibitory effects by the antagonists on its activation and cAMP production, carvedilol had significantly higher degree of inhibitory effects than the other two β -blockers in Arg-389 β 1-adrenergic receptor. These data suggest that effects of b-blockers may differ in β 1-adrenergic receptor 389 allele. In an *in vitro* experiment with ventricle tissues isolated from patients with HF, β 1-Arg-389 homozygote had 4.3-fold greater contractility than β 1-Gly-389 carrier upon agonist stimulation [68]

Bengtsson *et al.* 2001 investigated the difference in blood pressure among genotype-discordant siblings revealed that siblings with Gly389 allele had significantly lower resting diastolic blood pressure than those homozygous for Arg389 [70]. Studies have generally

β blockers

Several studies have investigated in possible effects of β 1AR Arg389Gly polymorphism on blood pressure responses to β -blocker treatment in hypertensive patients (table 2). Concerning metoprolol, patients homozygous for Arg389 had a significant greater reduction in 24-hr and day-time diastolic blood pressure [61]. This result was reproduced again by Liu *et al.* 2006 and found that the decrease in systolic, diastolic and mean arterial blood pressure was significantly larger in patients homozygous for Arg389 variant [42]. On the other hand, this polymorphism did not show the genotype-dependent differences in antihypertensive response to atenolol [62-64].

reported that alone, the Ser49Gly polymorphism does not importantly influence response, but when considered in combination with the Arg389Gly polymorphism, it may be more informative than Arg389Gly alone (Johnson *et al.* 2003, Liu *et al.* 2006) [61, 42]

β -2 adrenergic receptor

β 2-adrenergic receptor are more widely distributed, including expression in the heart, vasculature, respiratory smooth muscle, kidney, adipose tissue and in the brain. The gene consists of one exon with 2, 033 bp located at chromosome 5q31-q32. Many studies have examined whether β 2 adrenergic receptor Arg16Gly or Gln27Glu polymorphism influences the susceptibility to hypertension or the risk for elevated blood pressure, but have yielded conflicting results. Most of studies didn't detect significant genotype associations. A few studies observed significant genotype effects; however, consistent results was not observed and it could not be elucidated which of the two variants is more strongly associated with hypertension [69, 71]

Diuretic

As per the JNC 7 guidelines diuretic was recommended as first line drug of choice in the treatment of hypertension [72]. Numerous candidate genes may predict individual response to diuretics, twelve different polymorphism with diuretic has been examined in ten studies and eight of these studies used hydrochlorothiazide. the ADD1 Gly460Trp and ACE I/D polymorphism have been extensively studied [73-75]. Two nested case-control studies both drew their samples from the Genetic Epidemiology of Responses to Antihypertensives (GERA) cohort: one was a study of 19 candidate genes (45 total polymorphisms) [76] the other a 100, 000-SNP GWAS [39]. The former study reported variants in sodium channel, non voltage-gated 1, γ -subunit (*SCNN1G*) and nitric oxide synthase 3 (*NOS3*) that were associated with differences in diastolic blood pressure (DBP) response after 4 weeks of hydrochlorothiazide treatment. The *SCNN1G* findings were novel, the authors offered no probable mechanism for the observed differences in response, but noted that this gene has been associated with essential hypertension.

α -adducin gene

Adducin is an α/α heterodimeric cytoskeletal protein of the actin-spectrin lattice that is involved in signal transduction. Point mutations in the α -adducin gene explain up to 50% of the difference

in blood pressure level between Milan normotensive and Milan hypertensive rats, a genetically hypertensive strain of rats in which increased renal sodium reabsorption plays a major pathophysiological role [78, 79]. Cusi and colleagues 1997 [73] reported linkage between markers at the human α -adducin locus and a gene contributing to hypertension and found that a variant allele, characterized by a glycine-to-tryptophan change at amino acid 460 of α -adducin (Trp460), was significantly more frequent in 477 hypertensive patients than in 332 normotensive control subjects they tested whether the Gly460Trp polymorphism was associated with differences in the antihypertensive response to diuretic treatment with furosemide (40 mg orally every 6 h for three doses) or hydrochlorothiazide (12.5-25 mg orally once daily for 8 weeks). In both protocols, the average blood pressure reduction was more than two times greater in heterozygotes carrying the Trp460 variant than in Gly460 homozygotes. These findings were further confirmed in a subsequent trial, supporting the contention that the α -adducin polymorphism may be useful in identifying a subset of 'salt-sensitive' hypertensive patients more responsive to diuretic therapy [73, 74]. Manunta *et al.* 2008 [79] performed single SNP association analysis and combination analysis on *ADD1* (Gly460Trp), *NEDD4L* (rs4149601), *WNK1* (5 SNPs) in a 4-week diuretic trial. They found *ADD1* 460Trp carriers had significantly greater BP reduction than Gly460 homozygotes. When considered together, there was a significant trend ($p = 0.008$) in decreases of systolic blood pressure (SBP) (ranging from -3.4 mm Hg to -23.2 mm Hg) for different combinations of genotypes.

Renin-angiotensin system genes

Hypertensive subjects carrying the Trp460 variant of α -adducin had lower mean plasma renin activity than Gly460 homozygotes [73, 79, 74] individuals with 'low renin' hypertension are more responsive to diuretic therapy than those with normal or high renin hypertension [80, 53, 81]. Variation in genes of the RAA system has also been investigated in relation to antihypertensive responses to ACE inhibitors, α -blockers, and calcium channel blockers. Among hypertensive patients treated with ACE inhibitors (captopril, enalapril, lisinopril or perindopril), the T235 allele of the angiotensinogen gene was associated with significantly greater systolic and diastolic blood pressure reductions [82, 83].

The insertion/deletion (I/D) polymorphism of the ACE gene was not associated with differences in blood pressure responses to ACE inhibitors, β -blocker (atenolol), or a dihydropyridine calcium channel blocker (nifedipine) [82, 84, 83, 85] nor was a polymorphism of the angiotensin II (AT) receptor type 1 gene (A1166 to C) associated with differences in blood pressure response to ACE inhibitors [82].

A silent polymorphism in exon 5 of the gene coding for the α subunit of GS-protein, which couples β -adrenoreceptors to cAMP production, was reported to be associated with differences in blood pressure response to β -blockers [86].

Calcium channel blockers

Drugs in this class block voltage-gated calcium channels in the heart and vasculature, thereby reducing intracellular calcium. In the heart, this results in decreased cardiac contractility and reduced cardiac output; in the blood vessels, this leads to decreased smooth muscle contraction and peripheral resistance. Calcium channel blockers fall into three subclasses: phenylalkylamines (e. g., verapamil), benzothiazepines (e. g., diltiazem) and dihydropyridines (e. g., amlodipine). Drugs in these subclasses vary in their relative effect on cardiac versus vascular calcium channels, with the dihydropyridines affecting smooth muscle more, phenylalkylamines relatively selective for the myocardium and benzothiazepines intermediate between the other two. Of all antihypertensive drug classes, calcium channel blockers have seen the greatest increase in pharmacogenetics studies in the past 4 years, and some of these early results are promising. Three SNPs *CACNA1C* had significant associations with treatment in a study of BP lowering with calcium channel blockers [87].

Potential clinical implications of β -blocker pharmacogenetics: who should be prescribed β -blocker therapy and which β -blocker will produce appropriate response

Data from several studies suggest that there is a genotype group that responds less favorably to β blocker therapy [88, 89]. In an adrenergic receptor polymorphism sub-study a small pharmaceutical company is seeking FDA approval of bucindolol, with the therapy targeted at patients with specific genotypes. They suggest that the patients with the genotypes of interest may have better outcomes with bucindolol than the currently used β -blockers, whereas for those with alternative genotypes, the current β -blockers would be preferred. The FDA submission will be of great interest to the pharmacogenetics research community as it will represent the first request for labeling in a specific genotype group during the drug approval process, outside of cancer. FDA approval of bucindolol, with an indication in specific genetic groups, may also sound the beginning of pharmacogenetic-guided therapy in cardiovascular disease.

CONCLUSION

Variation in individual response to antihypertensive treatment motivates a search for genetic factors associated with this variation. Knowledge of genetic factors that predict antihypertensive drug response may eventually enable clinicians to choose the most effective drug for each individual patient based on his or her genetic profile. This tailored therapy may help patients achieve better blood pressure control and may help to reduce the costs and adverse effects of antihypertensive therapy. The goal of personalized medicine is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Pharmacogenomics is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment and a patient's characteristics, such as gender, age and concomitant medication.

CONFLICT OF INTERESTS

Declared None

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