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REVIEW

Pharmacogenomics And Hypertension: Current Insights

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Abstract: Hypertension is a multifactorial disease that affects approximately one billion subjects worldwide and is a major risk factor associated with cardiovascular events, including coronary heart disease and cerebrovascular accidents. Therefore, adequate blood pressure control is important to prevent these events, reducing premature mortality and disability. However, only one third of patients have the effective control of blood pressure, despite several classes of antihypertensive drugs available. These disappointing outcomes may be at least in part explained by interpatient variability in drug response due to genetic polymorphisms. To address the effects of genetic polymorphisms on blood pressure responses to the antihypertensive drug classes, studies have applied candidate genes and genome wide approaches. More recently, a third approach that considers gene-gene interactions has also been applied in hypertension pharmacogenomics. In this article, we carried out a comprehensive review of recent findings on the pharmacogenomics of antihypertensive drugs, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and calcium channel blockers. We also discuss the limitations and inconsistences that have been found in hypertension pharmacogenomics and the challenges to implement this valuable approach in clinical practice.

Keywords: antihypertensive therapy, candidate genes, GWAS, gene-gene interactions, hypertension, pharmacogenomics

Introduction

Cardiovascular disease is the leading global cause of death, accounting for approximately 17 million deaths annually.[1] Hypertension is one of the most common cardiovascular diseases and it is a major risk factor for coronary heart disease and cerebrovascular accidents, which can lead to premature mortality, morbidity and significant economic costs.[2] Studies indicate that within the next 20 years, the number of individuals affected by hypertension will increase by 60% to a total of more than 1.5 billion subjects.[3] Despite the increasing public awareness of hypertension and its complications, the rates of adequate blood pressure control (<140/90 mmHg) among patients receiving antihypertensive therapy remain unsatisfactory.[4] The reasons for these disappointing outcomes are complex, but include medication non-adherence, which may be due to adverse effects or treatment costs, and interindividual genetic variability.[5]

Indeed, genetic factors can affect blood pressure increases by 30–50%.[6,7] Therefore, over the past two decades, many genetic studies have aimed to clarify the causal genes of hypertension. In these studies, several genetic polymorphisms, including single nucleotide polymorphisms (SNPs), variable number of tandem

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repeats, microsatellites and insertions/deletions (I/D), were found associated with hypertension.[8] Moreover, these studies have shown that genetic factors are involved not only in the blood pressure elevation, but also contribute to the large interindividual variability in response to antihypertensive treatment, opening a window of opportunity for pharmacogenomic investigation and potential individualization of drug therapy.[5] In fact, considering the low rates of blood pressure control, the ability to identify the most effective antihypertensive agent for an individual patient prior to initiation of therapy has potential to be beneficial.[9] Successful examples of targeted antihypertensive therapy based on genetics include the personalized treatments available for most forms of monogenic hypertension.[10,11] Regarding essential hypertension, the risks of a genetic-guided approach for prescription of antihypertensive drugs would be relatively low, considering that the current method for selection of antihypertensive therapy is predominantly empirical, and frequently involves a trial and error approach to find the optimal regimen for a given patient.[9] Thus, the goal of hypertension pharmacogenomics is to use genetic information, in addition to other pertinent clinical or demographic parameters, to select the right antihypertensive therapy and the most favorable dose to maximize the drug efficacy and reduce the risk for adverse effects.[5]

In order to identify potential genetic predictors of antihypertensive responses, two main approaches have been applied: a hypothesis-driven approach on the candidate genes, encoding proteins involved in signaling pathways affected by antihypertensive drugs, and an unbiased hypothesis-free approach with genome-wide association studies (GWAS), supported by the randomness basis of frequentist statistics.[12,13] During the past decade, GWAS have overcome the application of candidate gene approach, resulting in the identification of several previously unknown candidate loci or genes, but the advantages and limitations of this method in hypertension pharmacogenomics compared to the hypothesis-driven approach are still under debate.[13] In addition to these strategies that focus on single-locus analysis, a third approach that takes into account gene-gene interactions has been recently applied in pharmacogenomic studies.[14] This strategy considers the biological complexity underlying drug response and evaluate potential epistatic interactions that may predict how a patient will respond to a given treatment.[15] In this review article, we summarize the recent findings on the pharmacogenomics of antihypertensive drugs and discuss current insights and future directions of this field.

Studies On The Pharmacogenomics Of Hypertension

Here, we review the pharmacogenomics of the most commonly prescribed antihypertensive agents in clinical practice, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and calcium channel blockers. A search was performed in the PubMed database for original articles focusing on the effects of genetic polymorphisms on blood pressure responses to the antihypertensive drug classes described above. The search terms used were: "Antihypertensive therapy", "Pharmacogenomics and Pharmacogenetics", "[each antihypertensive drug class] and pharmacogenomics". The literature search was limited to full-text articles in the English language. In addition, the reference lists of identified articles were searched for further papers.

Diuretics

Diuretics are the first-line drugs of choice for most patients with hypertension.[2] Their mechanism of action involves the increases in sodium excretion (natriuresis) and decreases in extracellular volume, leading to a reduction in cardiac output. Although the initial antihypertensive effects of these drugs are in fact due to diuresis, their long-term effects are maintained due to decreases in vascular resistance, possibly resulted from an inhibition of sympathetic nervous and/or renin-angiotensin systems.[16] Given the different mechanisms underlying the effects of diuretics, several candidate genes may predict individual responses to these drugs.

The most commonly used diuretic is the thiazide diuretic hydrochlorothiazide, which acts by inhibiting the sodium chloride cotransporter expressed in the distal convoluted tubule of the nephron.[17] Considering the substantial inter-individual variation in the antihypertensive responses to hydrochlorothiazide, a large number of studies has evaluated polymorphisms in candidate genes or in GWAS as predictors of blood pressure responses to this drug (Table 1). In this regard, the *ADD1* gene was one of the first candidate genes examined for antihypertensive responses to thiazide diuretics.[18,19] The *ADD1* gene encodes α-adducin, a cytoskeleton-associated protein that modulates ion transport.[20] Interestingly, it was found that carriers of the Trp allele for the Gly460Trp (rs4961)

Table 1 Summary Of Studies On The Pharmacogenomics Of Diuretics

Gene	Polymorphism	Study Type	Study Population	Main Findings	Reference
ADD1	rs4961	Candidate gene	Caucasians (n=58)	Trp allele carriers have lower renin levels and better responses to hydrochlorothiazide treatment	19
ADD1	rs4961	Candidate gene	Caucasians (n=268)	Change in ionic transport across the cell membrane with consequent decreased blood pressure in Trp allele carriers	21
ADD1	rs4961	Candidate gene	Caucasians (n= 87)	460Trp allele carriers have better responses to hydrochlorothiazide	22
ADD1	rs4961	Candidate gene	Caucasians (n=396)	Polymorphism did not modify blood pressure levels after use of diuretics	24
GNB3	rs5443	Candidate gene	African Americans (n=197) and Caucasians (n=190)	T allele carriers have better responses to hydrochlorothiazide	27
GNB3	rs5443	Candidate gene	Caucasians (n=39)	T allele carriers have better responses to hydrochlorothiazide	28
eNOS	Glu2983Asp	Candidate gene	African American (n=289) and Caucasians (n=290)	GG genotype carriers have better responses to hydrochlorothiazide, with decreased diastolic blood pressure	29
NEDD4L	rs4149601	GWAS	Caucasians (n=5152)	G allele carriers have better responses to hydrochlorothiazide	36
NEDD4L	rs4149601 and rs292449	GWAS	Caucasians (n=768)	G-C haplotype carriers have better responses to hydrochlorothiazide	37
Chromosome 12q	rs317689, rs315135 and rs7297610	GWAS	African Americans (n= 194) and Caucasians (n= 195)	ATT and ATC haplotypes carriers have worse responses to hydrochlorothiazide	38
Chromosome 12q	rs317689, rs315135 and rs7297610	GWAS	African Americans (n=147) and Caucasians (n=224)	ATT haplotypes carriers have worse responses to hydrochlorothiazide	39
BEST	rs61747221	GWAS	African Americans (n=242) and Caucasians (n=119)	A allele carriers have better responses to hydrochlorothiazide	40
PRKCA	rs16960228	GWAS	Caucasians (n=228)	A allele carriers have better responses to hydrochlorothiazide and higher baseline PRKCA expression	23
VASP	rs10995	GWAS	Caucasians (n=228)	G allele carriers have better blood pressure responses to hydrochlorothiazide and increased mRNA expression of *VASP*	42
ALDH1A2	rs261316	GWAS	Caucasians (n=314)	T allele was associated with uncontrolled blood pressure following treatment with a thiazide diuretic/β-blocker combination	43

polymorphism in the *ADD1* gene showed a reduced baseline plasma renin activity and a better antihypertensive response to hydrochlorothiazide treatment compared to Gly/Gly homozygotes.[19] A subsequent study found evidence suggesting that the rs4961 polymorphism may modulate renal sodium handling by changing ion transport

across the cell membrane.[21] While the association between rs4961 polymorphism and the antihypertensive responses to thiazide diuretics has been confirmed by some later studies,[22] lack of association was observed in others.[23,24]

Another gene that has been evaluated for hydrochlorothiazide responses is *GNB3*, which encodes β3-subunit of the G-protein.[25] This family of proteins is critical for many physiological and pharmacological responses once they mediate signal transduction from membrane receptors to a wide range of intracellular effectors.[25] Interestingly, it was reported that the T allele for C825T (rs5443) polymorphism in the *GNB3* gene is related to an RNA splice variant that lacks the nucleotides 498–620 of exon 9, resulting in structural modifications in the β3-subunit of G-protein and potentially affecting signal transduction.[26] Indeed, the T allele for this polymorphism was associated with better antihypertensive responses to hydrochlorothiazide with a gene-dose effect,[27] and this association was further confirmed by an independent study.[28] However, another study with a larger sample size failed to replicate these findings,[29] and therefore the association between the rs5443 polymorphism and hydrochlorothiazide responses remains unclear.

Given that the antihypertensive effects of diuretics are in part due to renin-angiotensin system inhibition,[16] some studies have tested whether polymorphisms in the gene encoding the angiotensin converting enzyme (*ACE*) affect the responses to these drugs. In a study evaluating the I/D polymorphism in intron 16 of *ACE* gene in 87 never-treated hypertensive patients, Sciarrone et al found that individuals carrying the I/I genotype had better antihypertensive responses to hydrochlorothiazide compared to those carrying the D/D genotype.[22] A later study in the Han Chinese population showed that this polymorphism affects hydrochlorothiazide responses in a gender-specific manner, since better antihypertensive effects were observed in men carrying the D/D genotype and women carrying the I/I genotype.[30] These associations were not replicated in a study including 208 hypertensive Finnish men.[31]

The *NEDD4L* has also been considered a candidate gene for hydrochlorothiazide responses. This gene encodes a ubiquitin ligase that targets the epithelial sodium channel for degradation, therefore affecting sodium reabsorption in the distal nephron.[32] Consistent with its function, studies have shown that polymorphisms in *NEDD4L* gene affect salt sensitivity, plasma renin concentrations and susceptibility to hypertension.[33–35] To test the effects of *NEDD4L* variants on the responses to antihypertensive drugs, the NORDIL (Nordic Diltiazem) Study evaluated Caucasian hypertensive patients randomized to beta-blockers or thiazide diuretics and followed-up for six months.[36] Interestingly, it was found that G allele carriers for the rs4149601 polymorphism in *NEDD4L* gene have better antihypertensive responses to hydrochlorothiazide and β-blockers than patients with the AA genotype.[36] These results were significantly replicated in white subjects in subsequent studies.[37] In addition, better blood pressure responses to hydrochlorothiazide was observed in white hypertensive patients carrying increasing copies of the G-C haplotype of *NEDD4L* gene (for the SNPs rs4149601 and rs292449, respectively).[37] These findings, however, were not replicated in African Americans.[37]

The Genetic Epidemiology of Responses to Antihypertensives (GERA) study was the first GWAS on the pharmacogenomics of hypertension therapy.[38] While no significant associations were observed in Caucasians, this study identified a region of chromosome 12q associated with the antihypertensive responses to hydrochlorothiazide in African Americans. The authors found that haplotypes on this chromosome composed by SNPs rs317689, rs315135, rs7297610 near lysozyme (*LYZ*), YEATS domain containing 4 (*YEATS4*), and fibroblast growth receptor substrate 2 (*FRS2*) were significantly associated with diastolic blood pressure responses to hydrochlorothiazide. The ATT and ATC haplotypes composed by these SNPs were more frequent in poor responders than in good responders. The SNP rs7297610 had the most significant individual value, and it was suggested to drive the observed association. Consistently, these results were replicated in an independent population of 291 African-Americans and 294 Caucasians,[38] therefore validating the findings. Interestingly, these results were also replicated in a later study enrolling 746 hypertensive subjects from Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR) study,[39] suggesting that haplotypes composed by SNPs rs317689, rs315135, rs7297610 may be potential predictors of hydrochlorothiazide responses. In addition, the chromosome 12q was recently re-sequenced in participants from GERA and PEAR studies and a novel missense SNP, rs61747221 in the *BEST3* gene was significantly associated with blood pressure responses to hydrochlorothiazide treatment.[40] In this study, subjects carrying AA

+AG genotypes for this polymorphism showed better antihypertensive responses to hydrochlorothiazide compared to GG carriers.

In order to identify novel genes affecting the antihypertensive responses to hydrochlorothiazide, Turner et al conducted genome-wide association meta-analyses combining the results from independent white hypertensive populations: PEAR, GERA, NORDIL, and Genetics of Drug Responsiveness in Essential Hypertension Study (GENRES).[23] By using this approach, they provided substantial evidence of associations between the SNP rs16960228 in *PRKCA* gene and blood pressure responses to hydrochlorothiazide. The A-allele carriers showed consistently better antihypertensive responses to this drug. Moreover, this study provided functional evidence that the A-allele for the SNP rs16960228 is associated with higher baseline *PRKCA* expression.[23]

More recently, several novel SNPs have been associated with blood pressure responses to hydrochlorothiazide in GWAS. Hiltunen et al identified four new SNPs affecting hydrochlorothiazide response (rs3825926, rs4867623, rs321329 and rs321320) in subjects from GENRES, PEAR and GERA studies.[41] Another GWAS including individuals from PEAR and PEAR-2 studies tested 1082 SNPs, prioritized according to their biological function, using RegulomeDB, haploreg and GWAVA software packages.[42] The results from the prioritization analysis showed the SNP rs10995 in the *VASP* gene (encoding the vasodilator-stimulated phosphoprotein) as the most likely functional SNP, among SNPs tested, that has been associated with hydrochlorothiazide responses. The G allele for this SNP was associated with greater blood pressure responses to hydrochlorothiazide and increased mRNA expression of *VASP*.[42] Consistently, these findings were replicated in an independent cohort treated with the thiazide diuretic chlorthalidone, thus validating the associations.[42] Also employing a GWAS approach, Magvanjav et al found that the SNP rs261316 in the *ALDH1A2* gene was associated with uncontrolled blood pressure following treatment with a thiazide diuretic/β-blocker combination in white participants of the PEAR study.[43] These findings were further validated in a replication study including subjects from INVEST study.[43] Taken together, these findings highlight GWAS as an efficient approach to identify novel polymorphisms involved with the antihypertensive responses to hydrochlorothiazide. Further studies are still required to confirm the functional relevance of the SNPs identified in the mentioned GWAS.

β-Blockers

Although β-blockers are no longer considered as first-line antihypertensive pharmacotherapy by the Joint National Committee (JNC8) hypertension guidelines,[2] they are still widely prescribed and retain an important place in the management of hypertension for certain subgroups of patients.[44] β-blockers decrease myocardial contractility, heart rate and cardiac output.[45] In addition to the cardiac effects, the antihypertensive effects of these drugs result from the blockage of their targets on juxtaglomerular cells of the kidney, decreasing renin secretion and thereby leading to a reduced production of circulating angiotensin II.[45,46]

The primary protein target of all β-blockers is the β1-adrenergic receptor, encoded by *ADRB1*.[47] This gene contains two common and widely studied genetic polymorphisms that lead to changes in the encoded amino acids: rs1801252, which leads to a serine to glycine change at the position 49 of the protein (Ser49Gly), and rs1801253, which results in the arginine to glycine change at the position 389 of the protein (Arg389Gly).[47] These two polymorphisms show important evidence for functional impact once they affect intracellular signaling mediated by the β1-adrenergic receptor.[48] Indeed, the ancestral alleles (Ser49 and Arg389) for these polymorphisms are both associated with improved intracellular responses to β1-adrenergic receptor agonists compared to variant alleles.[48] Despite the functional relevance, there is no consensus for the association between Ser49Gly or Arg389Gly polymorphisms and antihypertensive responses to β-blockers (Table 2). In a study including white, African American, and Hispanic individuals, carriers of Arg/Arg genotype for Arg389Gly polymorphism had better blood pressure responses to the β-blocker metoprolol compared to subjects carrying the Gly allele.[49] In addition to the genotypic findings, the authors observed that the haplotypes composed by Ser49Gly and Arg389Gly polymorphisms affect the blood pressure responses to metoprolol. Similar results were also found in Chinese hypertensive patients treated with the β-blocker carvedilol.[50] In the opposite direction, Chen et al recently reported that subjects carrying the Gly/Gly genotype for Arg389Gly polymorphism show greater antihypertensive responses to metoprolol.[51] Regardless of these positive findings, lack of association between Ser49Gly or Arg389Gly polymorphisms and blood pressure responses

Table 2 Summary Of Studies On The Pharmacogenomics Of β-Blockers

Gene	Polymorphism	Study Type	Study Population	Main Findings	Reference
ADRB1	rs1801253	Candidate gene	Caucasian (n=29), African American (n=10) and Hispanic (n=1) population	Arg/Arg genotype carrier have better blood pressure responses to metoprolol	49
ADRB1	rs1801253	Candidate gene	Chinese population (n=86)	Arg/Arg genotype carriers have better blood pressure responses to carvedilol	50
ADRB1	rs1801253	Candidate gene	Chinese population (n=261)	Gly/Gly genotype carriers have greater antihypertensive responses to metoprolol	51
ADRB1	rs1801252	Candidate gene	Caucasians (n=233)	Ser49Ser homozygotes showed a non-significant tendency to have a better response to bisoprolol	52
ADRB1	rs1801253 or rs1801252	Candidate gene	Caucasians (n = 340)	There was no association of the polymorphisms with the blood pressure response to atenolol	53
CYP2D6	*4	Candidate gene	Caucasians (n= 1533)	* 4/4 * genotype carriers have better blood pressure responses to metoprolol	57
CYP2D6	*3, *4, others	Candidate gene	Caucasians (n=84)	There was association of the polymorphisms with the blood pressure response to metoprolol	58
CYP2D6	*2,*3, others	Candidate gene	African Americans (n=84), European Americans (n=125), Asians (n=1) and others (n=8)	There was no association between *CYP2D6* variants and blood pressure responses to metoprolol	60
CYP2D6	rs1065852	Candidate gene	Chinese population (n=93)	There was no significant association between CYP2D6 gene polymorphisms and treatment outcome with metoprolol	61
CYP2D6	*2, *3, others	Candidate gene	White (n=39), black (n=9) and Latino-Hispanic (n=2) population	There was no significant association between CYP2D6 variants and blood pressure responses to metoprolol	62
SLC25A31	rs201279313	GWAS	African Americans (n=318)	Heterozygous patients have better antihypertensive responses to β-blockers	63
FGD5	rs294610	GWAS	Caucasians (n=201)	A allele carriers have better blood pressure responses to metoprolol	64
SLC4A1	rs45545233	GWAS	Caucasians (n=434)	C allele carriers have worse responses to β-blockers	64
ACY3	rs2514036, rs948445, and rs2514037	GWAS	Caucasians (n=228)	The SNPs rs2514036, rs948445, and rs2514037 are associated with blood pressure responses to bisoprolol	41
BST1	rs28404156	GWAS	Caucasians (n=1254)	A allele carriers have better blood pressure responses to β-blockers	66
KLOTHO	rs36217263	GWAS	Filipinos (n=76)	Deletion of at least one copy of allele A for rs36217263 in the *KLOTHO* gene is associated with poor response to β-blockers	67

to β-blockers was reported in two European prospective studies.[52,53]

In addition to polymorphisms in genes that modulate the pharmacodynamics of β-blockers, variants in genes

regulating their pharmacokinetics are also potential candidates to impact the antihypertensive responses to these drugs. One of these candidates is the gene encoding the cytochrome enzyme CYP2D6, which is a major responsible for metabolizing β-blockers.[42] Because there are evidences suggesting that the *CYP2D6* polymorphisms affect the pharmacokinetics of β-blockers,[54–56] some studies have evaluated whether these variations translate into variability in their effects. In fact, there are studies showing associations of *CYP2D6* genotypes and blood pressure responses to β-blockers.[57,58] Based on these evidences, the Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association has established therapeutic dose recommendations for metoprolol based on *CYP2D6* genotypes.[59] However, other studies have suggested that there is no sufficient evidence for the clinical utility of *CYP2D6* genotyping to guide metoprolol therapy in hypertension,[60] since lack of association between *CYP2D6* variants and blood pressure responses to this drug and other β-blockers has been observed in some studies.[56,60–62]

Recently, several GWAS have found polymorphisms affecting blood pressure responses to β-blockers (Table 2). Using this approach, Gong et al evaluated 318 African-American hypertensive participants from PEAR and PEAR-2 studies treated with β-blockers and observed that individuals carrying one variant allele (a deletion in the intronic region) for the SNP rs201279313 in *SLC25A31* gene (which encodes ADP/ATP translocase 4) have better antihypertensive responses to β-blockers compared to subjects carrying two wild-type alleles.[63] Moreover, they also found that subjects carrying the deletion allele of rs11313667, located in the intronic region of *LRRC15* gene (encoding leucine rich repeat containing 15) show greater blood pressure responses to β-blockers compared to individuals carrying two wild-type alleles. Importantly, these associations were replicated in an independent cohort of PEAR study,[63] thereby validating these findings.

Given that black subjects have different antihypertensive responses to β-blockers compared to Caucasians, recent GWAS have focused on this last population.[41,64,65] Hiltunen et al identified the SNPs rs2514036, rs948445, and rs2514037 in the *ACY3* gene (coding for aminoacylase III) associated with blood pressure responses to the β-blocker bisoprolol in Caucasians.[41] In a later replication study, only the SNP rs2514036 was found associated with blood pressure responses to atenolol.[65] Another GWAS evaluating European-Americans participants from PEAR-2 study found that the A allele carriers for rs294610 polymorphism in the *FGD5* gene (which encodes for FYVE, RhoGEF and PH Domain Containing 5) show better blood pressure responses to β-blockers. Consistently, these findings were replicated in European-Americans participants from PEAR study. In a secondary replication approach, the authors performed a meta-analysis between PEAR-2 and PEAR studies with an independent cohort from PEAR and identified an additional single nucleotide polymorphism (rs45545233) in the *SLC4A1* gene (encoding for Solute Carrier Family 4 Member 1) associated with poor responses to β-blockers.[64] More recently, Singh et al carried out a GWAS involving 5 randomized clinical trials consisting of 1254 patients with hypertension of European ancestry and identified A allele for the SNP rs28404156 in the *BST1* gene associated with better blood pressure responses to β-blockers.[66] Consistently, these findings were successfully replicated in 3 additional randomized clinical trials.[66]

In addition to African Americans and European-Americans, recent studies have used GWAS approach to identify genetic polymorphisms associated with blood pressure responses to atenolol in other populations. This is the case of a study performed by Sy et al, which investigated the association of genetic variants with antihypertensive responses to β-blockers among Filipinos.[67] Interestingly, they found that the deletion of at least one copy of allele A for rs36217263 polymorphism in the *Klotho* gene is associated with poor response to β-blockers. Further studies are required to test if these findings can be replicated in independent cohorts of Filipino subjects.

Angiotensin-Converting Enzyme Inhibitors And Angiotensin II Receptor Blockers

The renin-angiotensin system is well known for its modulation of the blood pressure and sodium homeostasis.[68] These effects are coordinated through integrated mechanisms in the kidney, cardiovascular system and the central nervous system.[68] The cascade that results in the physiologic effects of renin-angiotensin system involves the renin-mediated conversion of angiotensinogen into angiotensin I, which is further cleaved by angiotensin-converting enzyme (ACE), to produce angiotensin II, the final effector of the system.[69] Angiotensin II directly regulates blood pressure by stimulating angiotensin II type 1 receptor (AT1R) receptors present in the vasculature, kidney and central nervous system,

leading to vasoconstriction, sodium reabsorption, and increases in sympathetic tone.[69]

Two different classes of drugs targeting the renin-angiotensin system are widely prescribed to treat hypertension: ACE inhibitors, which preclude the formation of angiotensin II, and angiotensin II receptor blockers (ARB), which bind to AT1R, thereby antagonizing the effect of angiotensin II. Not surprisingly, genes encoding components of the renin-angiotensin system are the most likely candidate genes for a pharmacogenomic approach on these drugs (Table 3). The most studied polymorphism of these genes is the I/D in intron 16 of *ACE*.[70] Indeed, D allele of this polymorphism seems to be associated with higher levels of ACE in Caucasian[71] and Asian[72,73] populations, but not in African-Americans.[74] Accordingly, this allele has also been associated with cardiovascular[75–78] and renal[79,80] disease. However, conflicting results have been found regarding to the antihypertensive responses to ACE inhibitors or ARB. This is because the D allele was associated with better antihypertensive responses to these drugs in some studies,[81,82] while the I allele was associated with those effects in others;[83–85] in addition, several studies have shown no effects of this polymorphism on blood pressure responses to ACE inhibitors or ARB.[86–89] Many factors, including study population, sample size, and possible interethnic differences in the distribution of I/D *ACE* polymorphism could explain these discrepancies.

Other candidate genes that are part of the classical cascade of the renin-angiotensin system and therefore could affect the antihypertensive responses to ACE inhibitors and ARB include *AGT* and *CYP11b2* genes. The *AGT* gene encodes angiotensinogen, and the most studied polymorphism of this gene is the SNP Met235Thr (rs699), which results in a threonine instead of a methionine in codon 235 of the protein.[90] However, similar to the I/D polymorphism in *ACE* gene, there is no consensus regarding the effects of this polymorphism on the antihypertensive responses to ACE inhibitors or ARB.[85,87–89,91,92] The *CYP11b2* gene encodes aldosterone synthase, the enzyme that catalyzes the final step of aldosterone synthesis in juxtaglomerular cells.[93] One important polymorphism in this gene is the SNP −344C/T (rs179998), which was shown to affect aldosterone levels and hypertension susceptibility.[94–97] Interestingly, the −344C/T polymorphism has been found associated with blood pressure responses to ARB,[92,98–100] although it is still not clear which variant contributes to greater responses. In fact, while this effect was attributed to the C allele of this SNP in some studies,[99,100] the same effect was associated with the T allele in others.[92,98] Studies with larger populations are required to interpret the findings more conclusively.

In addition to the renin-angiotensin system inhibition, the beneficial effects of ACE inhibitors and ARB are associated with several pleiotropic effects.[101–103] Indeed, many of these effects are related to the vasodilation produced by nitric oxide (NO) as a result of endothelial NO synthase (NOS3) activation.[104,105] NOS3 is the dominant NO synthase in the vasculature and polymorphisms in the gene encoding this enzyme have been associated with hypertension and other cardiovascular alterations.[106–108] The pharmacogenomic relevance of NOS3 for ACE inhibitor and ARB responses has been shown in different studies. One of these studies focused on hypertensive patients treated with the ACE inhibitor enalapril.[109] This study observed higher frequencies of the C allele for the *NOS3* SNP −786T/C (rs2070744) in patients with good responses to this drug as compared with those patients classified as poor responders.[109] In line with these findings, another study showed that the ARB olmesartan promotes increased NO formation in endothelial cells that are homozygous for C allele of this polymorphism compared to heterozygous cells.[110] Therefore, both enalapril and olmesartan seem to have more significant effects in the presence of C allele for −786T/C polymorphism, suggesting that hypertensive subjects carrying this allele may have better responses to these drugs. More recently, the T allele for the *NOS3* SNP −665C/T (rs3918226) was associated with greater responses to enalapril, whereas the A allele for the *NOS3* tagSNP rs3918188 and the CAG haplotype involving *NOS3* tagSNPs were associated with the opposite effect.[111] Additionally, different proteins have been described to contribute to NOS3 activation promoted by ACE inhibitors, including bradykinin receptor B2 (BDKRB2), protein kinase C (PKC) and vascular endothelial growth factor (VEGF).[105,112,113] Taken this into consideration, we have recently shown that polymorphisms in genes encoding BDKRB2, PKC and VEGF affect the antihypertensive responses to the enalapril[109,114,115] (Table 3). Taken together, these findings clearly suggest that genetic variability in *NOS3* gene or in genes that contribute to NOS3 activation may affect the responses to ACE inhibitors and ARB.

In addition to the candidate gene approach, GWAS have also identified genetic predictor of response to drugs targeting the renin-angiotensin system (Table 3). This is the case of a study enrolling 372 Italian hypertensive subjects treated with the ARB losartan and further

Table 3 Summary Of Studies On The Pharmacogenomics Of Angiotensin-Converting Enzyme Inhibitors And Angiotensin II Receptor Blockers

Gene	Polymorphism	Study Type	Study Population	Main Findings	Reference
ACE	Insertion/ Deletion	Candidate gene	Malay population (n=144)	DD genotype carriers have greater response to enalapril or lisinopril than ID and II genotypes	81
ACE	Insertion/ Deletion	Candidate gene	Greek population (n=104)	DD genotype carriers have greater response to fosinopril	82
ACE	Insertion/ Deletion	Candidate gene	Caucasians (n=86)	I allele carriers have greater response to irbesartan, with reduction in diastolic blood pressure	83
ACE	Insertion/ deletion	Candidate gene	Japanese population (n=57)	DD or ID genotype carriers have greater the plasma ACE activity and better response to imidapril	84
ACE	Insertion/ deletion	Candidate gene	Malay population (n=142)	I allele carriers have better response to lisinopril or enalapril, with decreased systolic and diastolic blood pressure	85
ACE	Insertion/ deletion	Candidate gene	Japanese population (n=60)	DD genotype carriers have greater response to enalapril	86
ACE	Insertion/ deletion	Candidate gene	Caucasians (n=102)	There were no associations with ACE inhibitors treatment outcome	87
ACE	Insertion/ deletion	Candidate gene	Caucasians (n=63)	There was no significant association of the polymorphisms with the blood pressure response to atenolol, lisinopril and nifedipine	89
CYP11B2	rs179998	Candidate gene	Caucasians (n=86)	TT genotype carriers have better response to irbesartan	98
CYP11B2	rs179998	Candidate gene	Chinese population n=98	CC+CT genotype carriers have better response to valsartan	99
NOS3	rs2070744	Candidate gene	Brazilian population (n=106)	C allele carriers have better response to enalapril	109
NOS3	rs2070744	Candidate gene	Human umbilical vein endothelial cells were isolated into primary cultures from Caucasian n=18	Homozygous endothelial cells for the allele C have better response to olmesartan, with increased NO formation	110
NOS3	rs3918188	Candidate gene	Brazilian population (n=101)	Carriers of AA genotypes of rs3918188 have worse response to enalapril	111
NOS3	rs3918188	Candidate gene	Brazilian population (n=101)	Carriers of AGG haplotype have better response to enalapril	111
BDKRB2	rs1799722	Candidate gene	Brazilian population (n=106)	Carriers of TT genotype is associated with worse response to enalapril	109
BDKRB2/ PRKCA/NOS3	rs1799722	Candidate gene	Brazilian population (n=104)	Epistatic interaction where carriers of GG of rs16960228 (*PRKCA*), TC or TT of rs2070744 (*NOS3*) and CC of rs1799722 (BDKRB2) are associated with worse response to enalapril	114

(*Continued*)

Table 3 (Continued).

Gene	Polymorphism	Study Type	Study Population	Main Findings	Reference
PRKCA	rs16960228	Candidate gene	Brazilian population (n=104)	GG genotype carriers have better response to enalapril, with a decrease in mean and diastolic blood pressure	114
VEGFA	rs699947, rs1570360 and rs2010963	Candidate gene	Brazilian population (n=102)	Carriers of CA and AA genotypes of rs699947 polymorphism and AGG haplotype have better response to enalapril	115
CAMK1D	rs10752271	GWAS	Caucasians (n=372)	GG genotype carriers have better blood pressure responses to losartan	116
SCNN1G	rs11649420	GWAS	White Americans (n=198)	GG genotype carriers have better response to candesartan	116
GPR83	rs3758785	GWAS	African Americans (n=193)	GG genotype carriers have better response to candesartan	117
FUT4	rs11020821	GWAS	White Americans (n=198)	The polymorphism rs11020821 is associated with better blood pressure responses to candesartan	117
Nphs1	rs3814995	GWAS	Caucasians (n=203)	The polymorphism rs3814995 (Glu117Lys) is associated with better blood pressure responses to losartan, with decreased systolic blood pressure	41

replicated in two independent populations.[116] In this GWAS, the authors found the GG genotype for the SNP rs10752271 in *CAMK1D* gene (encoding calcium/calmodulin dependent protein kinase 1D, involved in aldosterone synthesis) associated with better blood pressure responses to losartan.[116] Another GWAS identified multiple loci influencing antihypertensive response to the ARB candesartan in subjects from GERA study.[117] The associations were observed with the SNPs rs11020821 in *FUT4* gene (encoding fucosyltransferase 4), rs3758785 in *GPR83* gene (encoding G protein-coupled receptor 83), and rs11649420 in *SCNN1G* gene (encoding sodium channel, non-voltage-gated 1, gamma subunit).[117] Replication in independent populations is required to make these findings more robust. Additionally, a further GWAS involving GENRES participants found the SNP rs3814995 in *NPHS1* gene (encoding nephrin, a transmembrane protein that is a structural component of the slit diaphragm in the kidney and an important contributor to blood pressure regulation) associated with improved blood pressure responses to losartan.[41] Consistently, this association was also replicated in GERA2 and Italian hypertensive patients treated with the Angiotensin receptor blocker losartan (SOPHIA) populations.

Calcium Channel Blockers

Calcium channel blockers (CCB) constitute a heterogeneous class of drugs commonly prescribed to treat a wide array of cardiovascular conditions, including hypertension.[118] Although all agents in this class act by blocking calcium channels, each subclass binds at a specific location. While the subclass of dihydropyridines, such as nifedipine and amlodipine, has vascular selectivity, verapamil has cardiac selectivity, and diltiazem can act both in the heart and blood vessels.[45] Given that blood pressure responses to CCB are widely variable,[119] studies have investigated potential genetic polymorphisms that could contribute to this variability. Consistent with CCB mechanism of action, studies have shown that polymorphisms in genes encoding different ion channels, such as voltage-gated calcium channel α1C (*CACNA1C*), α1D (*CACNA1D*) and β2 (*CACNB2*), large-conductance calcium and voltage-dependent potassium channel β1 (*KCNMB1*), and ERG potassium channel (*KCNH2*) affect the antihypertensive responses to CCB or the risk of adverse cardiovascular outcomes[120–124] (Table 4).

In addition to explore polymorphisms in genes implicated in CCB pharmacodynamics, studies have also tested

Table 4 Summary Of Studies On The Pharmacogenomics Of Calcium Channel Blockers

Gene	Polymorphism	Study Type	Study Population	Main Findings	Reference
CACNB2	rs2357928	Candidate gene	Caucasians (n=2284)	Patients with GG genotype treated with verapamil have a higher risk of adverse cardiovascular outcomes.	120
KCNMB1	Val110Leu	Candidate gene	Caucasians (n=5979)	Leu110 allele is associated with a decreased risk of adverse outcomes among patients with hypertension and coronary artery disease	121
KCNMB1	Glu65Lys	Candidate gene	Caucasians (n=5979)	Lys65 allele carriers achieve blood pressure control earlier than Glu65Glu genotype	121
CACNA1D	rs312481	Candidate gene	Japanese population (n=161)	GG genotype carriers have better response to calcium channel blockers	122
CACNA1D	rs3774426	Candidate gene	Japanese population (n=161)	CT + TT genotypes carriers have better response to calcium channel blockers	117
CACNA1C	rs52797	Candidate gene	Japanese population (n=161)	GA + AA genotypes carriers have better response to calcium channel blockers	117
CACNA1C	rs2239050	Candidate gene	Caucasians (n=120)	GG genotype carriers have better response to amlodipine or felodipine	118
KCNH2	rs1137617	Candidate gene	Chinese population (n=370)	CT+TT genotypes carriers have better response to azelnidipine or nitrendipine, with decreased of systolic and diastolic blood pressure	124
CYP3A5	rs776746	Candidate gene	Chinese population (n=75)	CY3A5*3/3* genotype carriers have better response to amlodipine	129
CYP3A4	rs2246709	Candidate gene	African Americans (n= 164)	C allele carriers have better response to amlodipine	131
CYP3A5	CYP3A5 * 3, *6	Candidate gene	African Americans, Caucasians and Hispanics (n=722)	Blacks and Hispanic participants carrying the ancestral allele (*1) show better response to verapamil	132
PICALM	rs588076	GWAS	Japanese population (n=93)	C allele carriers of rs588076 have better response to amlodipine	133
TANC2	rs2429427	GWAS	Japanese population (n=93)	G allele carriers have better response to amlodipine	133
NUMA1	rs10898815	GWAS	Japanese population (n=93)	C alleles carriers have better response to amlodipine	133
APCDD1	rs564991	GWAS	Japanese population (n=93)	C alleles carriers have better response to amlodipine	133
PLCD3	rs12946454	GWAS	Caucasians (n=3863)	TT genotype carriers have better response to diltiazem treatment	134

the effects of variants in genes regulating CCB pharmacokinetics on the antihypertensive responses to these drugs. Calcium channel blockers are largely metabolized in the liver via the cytochrome P450 3A5 (CYP3A5),[125,126] and therefore, studies have examined if polymorphisms in the gene encoding this enzyme affect CCB responses. Contrary to the functional *CYP3A5*1* allele, the *CYP3A5*3* variant has a 6986A>G mutation in intron 3 that results in a splicing defect in CYP3A5 mRNA and a nonfunctional protein.[127] Another mutation (14690G>A) in exon 7 of *CYP3A5* gene (*CYP3A5*6*) also leads to a splicing defect and deletion of exon 7, thereby resulting in

a protein truncation.[127] Despite the role of CYP3A5 in CCB metabolism, the effects of these *CYP3A5* variants on CCB responses are not clear. Indeed, Zhang et al and Huang et al found the *CYP3A5*3* allele associated with better antihypertensive responses to the CCB amlodipine in the Chinese population.[128,129] However, no associations between *CYP3A5* variants and CCB effects were observed in Koreans[130] and African-Americans.[131] These discrepancies may be explained by the fact that amlodipine responses can be influenced by ethnicity as a result of genetic factors, environmental factors and their interaction.

Besides amlodipine, studies have also investigated the influence of *CYP3A5* polymorphisms on blood pressure responses to the CCB verapamil. Langaee et al addressed this question by using a haplotype approach, with any allele containing either (*3) or (*6) designated as nonfunctional.[132] The authors observed that the number of *CYP3A5* functional alleles was marginally associated with blood pressure responses to verapamil in blacks and Hispanics, but not in whites, with the effect being largely driven by worst responses in the carriers of two functional alleles.

Along with the candidate gene approach, some GWAS have shown SNPs associated with blood pressure responses to CCB (Table 4). Using this strategy, Kamide et al[133] found that the alleles C for rs588076, G for rs2429427, C for rs10898815 and C for rs564991 of the *PICALM, TANC2, NUMA1* and *APCDD1* genes, respectively, are associated with antihypertensive responses to CCB in Japanese hypertensive patients. Consistently, these findings were further replicated in an independent Japanese population.[133] Taking advantage of previous GWAS findings, another study identified the SNP rs12946454 of *PLCD3* gene (which encodes phospholipase C, delta 3) associated with blood pressure responses to the CCB diltiazem.[134] Interestingly, the authors found an additive effect for increasing copies of T allele for this SNP and more intense blood pressure reductions (1.53 mmHg per allele for systolic blood pressure and 0.73 mmHg per allele for diastolic blood pressure) after diltiazem treatment. However, replication of these findings in independent populations is still pending.

Gene-Gene Interactions In The Pharmacogenomics Of Hypertension

The two main approaches frequently used in pharmacogenomic studies (candidate gene and GWAS) evaluate associations between individual genes and the drug response. However, these approaches may overlook the associations that can only be detected when the combinations of multiple genomic regions are examined.[135,136] Indeed, a lot of the genetic predisposition to drug response phenotypes seems to be hidden in multigenic and multifactorial complex traits.[137] Therefore, novel approaches that consider the interactions among polymorphisms from different genes within drug response pathways should be considered in pharmacogenomic studies.

One of these approaches involves the use of the multifactor dimensionality reduction, a machine learning method that detects the high-order gene-gene interactions with the use of relatively small sample sizes.[138–140] Using this method, Silva et al showed that interactions between *NOS3* and *BDKRB2* polymorphisms affect the antihypertensive responses to enalapril.[109] Interactions between these genes are expected, as both proteins encoded by them are involved in the same signaling pathway modulated by ACE inhibitors. Interestingly, it was found that, although the CC genotype for the rs1799722 *BDKRB2* polymorphism was not associated with the antihypertensive response to enalapril at single-locus analysis, gene-gene interaction analysis showed that the CC genotype for this polymorphism combined with the TT genotype for rs2070744 *NOS3* polymorphism was more frequent in poor responders to enalapril, while the combination of *BDKRB2* CC genotype with *NOS3* TC genotype was more frequent among good responders.[109] These findings are underestimated when single *BDKRB2* genotypes alone are analyzed, thus highlighting the relevance of gene-gene interaction analysis.

Following up on this study, we have recently investigated the involvement of *PRKCA* gene (encoding PKCα) in the interactions described above.[114] Interestingly, we described that such combinations between *BDKRB2* and *NOS3* genes found to be associated with antihypertensive responses to enalapril were significant only when combined with the GG genotype for the rs16960228 *PRKCA* polymorphism.[114] These gene-gene interactions are in line with the signaling cascade that, at least in part, contributes to the antihypertensive effects of ACE inhibitors.[105] The inhibition of ACE leads to enhanced bradykinin levels, which activate bradykinin receptors on endothelial cells.[105] The activation of these receptors stimulates PKCα, which then activates NOS3, resulting in vasodilation due to increased NO production.[113,141,142] The evaluation of circulating nitrite levels (a marker of endogenous NO formation) may be a possible approach to clarify the cellular

mechanisms underlying the effects of *BDKRB2, PRKCA* and *NOS3* interactions on enalapril responses. Indeed, *NOS3* polymorphisms were shown to affect plasma and blood nitrite concentrations.[106,107] However, additional studies are required to test the effects of gene interactions within this pathway on circulating nitrite levels in patients treated with ACE inhibitors. Taken together, these findings suggest that gene-gene interaction analysis is a promising approach that should be considered in the pharmacogenomics of hypertension.

Concluding Remarks And Future Directions

In this article, we have reviewed the recent pharmacogenomic literature for the main classes of antihypertensive drugs currently in use (i.e., diuretics, β-blockers, ACE inhibitors, ARB, and CCB). While a number of studies support an important contribution of genetic polymorphisms on blood pressure responses to antihypertensive therapy, some studies have failed to detect significant effects or replicate previous findings. These inconsistencies may be related to interethnic differences in the distributions of polymorphisms tested/identified, or to epigenomic alterations that could mask the contribution of DNA sequence variants.[143] Moreover, the inconsistencies may be attributed to heterogeneous phenotypes. In this case, variability in the etiology and mechanisms involved may explain the differences in observed phenotype, thereby reducing the possibility of successfully detecting associations between genetic polymorphisms and antihypertensive responses. Therefore, it is critical that subjects are carefully phenotyped and maybe surrogate markers of disease should also be examined. Another issue that can lead to inconsistent results is the effect of the previous treatments. The persisting antihypertensive effect after stopping therapy may preclude pharmacogenomic studies enrolling previously treated patients without an adequate washout period from getting reliable findings. To avoid this issue, studies should be preferentially performed in recently diagnosed patients that have never been treated before.

The inconsistencies and limitations observed in studies of pharmacogenomics of hypertension may be also dependent on the type of strategy applied. In fact, vast majority of studies discussed here applied two different approaches: gene candidate and GWAS. During the past decade, the shift from gene candidate approach to GWAS has been noteworthy. However, the large and inevitably heterogeneous sample size required for GWAS may preclude these studies from disentangling the complex genetics basis of hypertension, which consists of dynamic interactions among genetic/environmental aspects that may change with aging. This could help to explain the fact that some significant results found in candidate-gene studies, usually performed in more homogeneous cohorts, are not necessarily found in GWAS. On the other hand, the candidate gene approach prevents the identification of novel candidate loci or genes that could impact hypertension therapy. Taking this into consideration, Manunta et al propose to integrate the candidate gene with GWAS approach, in order to minimize their respective limitations.[13] A possible strategy to fully exploit the pharmacogenetic relevance of a given polymorphism and therefore increase the chances of defining clinically significant benefits would be testing the significant results found in GWAS in more homogeneous cohorts, in parallel with mechanistic studies to validate the biological significance of the pharmacogenetic findings.

Other than improving approaches that focus on single-locus analysis, another promising strategy to overcome the limitations of hypertension pharmacogenomics is the investigation of interactions among polymorphisms from different genes within drug response pathways.[14] Indeed, the polygenic nature of hypertension indicates that single loci may not be the best clinical target for all individuals.[144] The studies discussed in this article highlight the relevance of evaluating the interactions among multiple loci when studying complex traits, which is the case of antihypertensive response phenotypes. Given that these ideas are relatively new in the pharmacogenomics of hypertension, further studies in different populations are required to replicate the findings reported by the studies presented here. Another strategy that also takes into account the polygenic nature of hypertension is the use of genetic risk score (GRS). This approach has recently been developed to evaluate the impact of multiple blood pressure-associated variants on blood pressure levels, risk of hypertension, and other cardiovascular diseases.[145,146] Interestingly, GRS analysis showed that all blood pressure-elevating alleles combined could increase systolic blood pressure by 10 mm Hg and increase the risk of cardiovascular events.[145,146] Therefore, this seems to be a promising strategy to be used in future studies on hypertension pharmacogenomics.

Despite the issues described above, it is reasonable to suggest that data from several genes shown in the studies discussed in this review provide valuable genetic

information for hypertension pharmacogenomics research. In order to provide a realistic estimate on how much variation of responses to antihypertensive therapy may be explained by genetic markers, a systematic review and meta-analysis involving the recent studies on hypertension pharmacogenomics would be required. This would help to translate the research findings into clinical practice to improve hypertension therapy, which remains a challenge. In addition, given that a significant number of hypertensive patients require more than one drug to achieve the therapeutic goals, increasing the number of studies focusing on drug combinations, although not an easy task, would also help to approximate hypertension pharmacogenomics to the clinical practice. In fact, while a lot of progress was achieved in the clinical application of pharmacogenomics in oncology and anticoagulation therapy, the same has not been seen in hypertension therapy.[147] In this regard, antihypertensive agents do not have serious or lethal side effects such as those of anticancer drugs or warfarin. In addition, cancer is a condition where drug efficacy may have immediate influence on short-term survival. All these reasons may explain the lack of motivation in personalizing medicine for hypertension therapy, resulting in patients often taking an antihypertensive drug that is less effective than required. To start changing this paradigm, several academic medical centers are already piloting programs to implement hypertension pharmacogenomics in clinical practice.[148,149]

Indeed, an efficient pharmacogenomic strategy to get hypertensive patients on the most effective and well-tolerated drug regimen would be extremely valuable. This would result in less patient visits to readjust the treatment, fewer drugs per patient, and a more cost-effective approach than the trial and error in current practice. An adequate blood pressure control would prevent cardiovascular and renal events and improve the quality of life and longevity of hypertensive patients.

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Disclosure

The authors report no conflicts of interest in this work.

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