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Current updates on pharmacogenetics of hypertension

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Abstract

The leading cause of cardiovascular disease is hypertension, whereas less than half of the patients are on antihypertensive drugs to control their blood pressure. Hypertension is a complex condition that affects more than one billion population in the world. Therefore, controlled blood pressure helps to prevent any cardiovascular event and reduce premature mortality and disability. In a non-responsive hypertensive patient, pharmacogenomics helps to guide personalized treatment. Pharmacogenetics gives hope toward targeted therapy, but challenges remain in implementing pharmacogenetic-aided antihypertensive therapy in clinical practice. There is only a lower percentage of genetic variability in response to antihypertensive drugs that have been explained, and the vast majority of the genetic variants associated with antihypertensives efficacy and toxicity remain to be identified. Therefore, some genetic variants with evidence of association with the variable response related to these most commonly used antihypertensive drug classes needed to be confirmed in future studies.

Keywords: Beta blocker, Candidate genes, Diuretics, Gene-gene interactions, Hypertension,

Introduction

Hypertension is commonly diagnosed at the early or primary stage and if it is not managed properly, it can lead to strokes, renal infection, cardiovascular disease, and death (1). As per the American Heart Association/The American College of Cardiology (AHA/ACC), hypertension is characterized by a systolic blood pressure (SBP) of 130 mmHg or higher and/or diastolic blood pressure (DBP) of 80 mmHg or higher. Drug therapy should be initiated when systolic blood pressure is 140 mmHg or higher and/or diastolic blood pressure is 90 mmHg or higher, as per the AHA/ACC guidelines. Blood pressure increases by 30–50% which is affected by genetic factors. Numerous genetic polymorphisms have been associated with hypertension, including insertions/deletions (I/D), microsatellites, single nucleotide polymorphisms (SNPs), and variations in the frequency of tandem repeats (2,3,4).

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Table 1: Classification of blood pressure

Blood pressure	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normal	<120	<80
Elevated	120-129	<80
Stage 1 Hypertension	130-139	80-89
Stage 2 Hypertension	≥140	≥90

The genetic association between candidate genes and maker loci has been demonstrated in many studies that potentially influence BP. These genes play a role in regulating the blood pressure of an individual by coding channels, proteins, and drug metabolism enzymes (3).

Given the low rate of control of blood pressure, it may be advantageous to determine the more effective antihypertensive drugs for the patients before starting the therapy. Successful genetics-based targeted antihypertensive treatments include the individualized treatments available for most monogenic hypertension. Given that the current method for selecting antihypertensive treatment is primarily empirical and generally includes a trial-and-error method to discover the best regimen for a particular patient (1), the risks of a genetically guided approach for prescribing antihypertensive medications would be relatively minimal for essential hypertension (1). Therefore, the purpose of pharmacogenomics in hypertension is to use genetic information besides other relevant demographic or clinical parameters to select appropriate antihypertensive treatment with the most suitable doses to maximize the therapeutic efficacy and minimize the risk of adverse effects. Two basic approaches have been used to find out potential genetic determinants of antihypertensive responses: an objective, hypothesis-free method using genome-wide association studies (GWAS), supported by the randomization basis of frequent statistics (3), and a hypothesis-driven strategy on the candidate genes that encodes proteins which are involved in various signaling pathways altered by antihypertensive drugs (3). Over the last ten years, GWAS has outperformed the candidate gene technique, which resulted in the identification of several previously undiscovered candidate loci or genes. However, the benefits and drawbacks of this method in comparison to the hypothesis-driven approach in hypertension pharmacogenomics are still up for debate. A third strategy that considers gene-gene interactions has recently been used in pharmacogenomic studies besides previous single-locus analysis-focused methodologies. This approach takes into account the biological complexity that underlies drug response and assesses potential epistatic interactions that could foretell a patient's reaction to a particular course of treatment (5,6).

Inter-individual genetic variability is one of the reasons for abnormal responses to antihypertensive drugs. Over the past two decades, a number of studies have been focusing on pharmacogenetics and pharmacogenomics. Pharmacogenomics is a broader term used to describe all genes in the genome that may affect drug response (1,2,4). Although both terms are used

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interchangeably, pharmacogenetics will be used in this review. Single nucleotide polymorphisms (SNPs) are the most frequent variation in the human genome, which are constituted by the presence of two or more different nucleotides (alleles) at the same position in the general population. Some alleles may affect the quantity or the function of the protein coded by the gene. Therefore, some alleles may be of functional relevance, as they may affect the amount and/or activity of the gene products in the cells, and may change the drug's pharmacokinetics or pharmacodynamics. Pharmacogenetics claims to replace the "trial and error" approach with a personalized prescription approach which is based on each person's genetic profile, and it may favor the selection of the "right drug" and the most advantageous dose to maximize the benefit of the drug and decrease the incidence of adverse events. The goal of antihypertensive treatment is the prevention of adverse cardiovascular outcomes largely attributed to blood pressure (BP) control. The pathophysiology of BP regulation and hypertension at the molecular level is highly diverse, and essential hypertension involves a broad spectrum of mechanisms, proposing that the patient might benefit from a customized drug regimen and dosage once the defective mechanism is identified. Thus, the identification of those mechanisms underlying hypertension could contribute to individualized treatment by favoring BP control and that will reduce hypertension-related morbidity and mortality.

Genetic Polymorphisms Involved in Antihypertensive Therapy

Pharmacogenetics is a novel way to treat a disease that maximizes the therapeutic efficacy and minimizes the adverse effects of a drug in an individual. The genes which are linked to hypertension interact with antihypertensive drugs to alter the blood pressure response and increase the adverse effects risk (7,8). Currently, candidate gene studies, genome-wide linkage scans, and association studies have discovered common genetic variants which explain less than 3% of the observed variance of BP levels. Although the 1000 Genomes Project and the ENCODE Project have contributed to respectively annotate rare variants and likely causal variants. One reason for the delayed development in our understanding of the genetics of hypertension and the pharmacogenetics of aberrant responses to antihypertensive drugs is the complexity of the regulation of the genome and the heterogeneity of hypertension (1,5). Therefore, the identification of genetic variants related to BP regulation may reveal new drug targets for the treatment of hypertension.

Pharmacodynamics genetic polymorphisms interactions with antihypertensive drugs

Diuretics (2,5,6)

The first line drug of choice in most of the hypertensive patients is diuretics. The mechanism of action is increasing the sodium execration and decreasing the extracellular volume to reduce the cardiac output. In the long-term effect, it reduces vascular resistance and inhibits the sympathetic nervous and/or renin-angiotensin systems.

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Table 2: Key genetic variants associated with blood pressure (1,4,5,6,7,8)

Drug	Gene	Variant (s)	Clinical findings
Thiazides	NEDD4L	rs4149601	G allele associated with greater BP response, a better outcome with diuretics
	YEATS4	rs7297610	CC genotype greater BP response in African-Americans, with greater leukocyte expression of YEATS4 and greater decline after HCTZ treatment
	PKCA	rs16960228	A allele carriers carry greater BP response than GG genotype
	GNAS-EDN3	rs2273359	G allele carriers carry greater BP response than CC genotype
Beta-blockers	ADRB1	rs1801252	A allele (49Gly) has a greater DBP response, C allele (389Gly) has a greater DBP response, 49Ser-389Arg haplotype has mortality benefit in atenolol versus verapamil

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		rs1801253	
	GRK4	rs1024323	65Leu-142Val haplotype has a worse BP response to beta-blocker
		rs2960306	
		rs1801058	A allele (486Val) increases cardiovascular events
	PTPRD	rs12346562	A allele predicts SBP response to atenolol in the Caucasian population

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		rs10739150	G allele predicts SBP response to atenolol in African–Americans
	SLC25A31	rs201279313	Deletion allele predicts a greater DBP response in African-Americans
	LRRC15	rs11313667	Deletion allele predicts a greater SBP response in African-Americans
Metoprolol	CYP2D6		Poor metabolizers are more sensitive, and at risk for bradycardia
Verapamil	KCNMB1	rs11739136	65Lys achieves faster BP control with verapamil 110Leu protects against cardiovascular outcomes in the verapamil group
		rs2301149	
Losartan	NPHS1	rs3814995	A allele (117Lys) has greater SBP and DBP response

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The most commonly used diuretic is the thiazide diuretic hydrochlorothiazide, which acts by inhibiting the sodium chloride co-transporter expressed in the distal convoluted tubule of the nephron. Several studies have assessed the polymorphisms in GWAS or candidate genes as indicators of BP response to this medication. The ADD1 gene was one of the first potential genes studied for antihypertensive responses to thiazide diuretics, according to study by Glorioso N et al. and Cusi D et al (9,10,11). The ADD1 gene encodes the ion transport-regulating protein α - adducin, which is linked with the cytoskeleton. As opposed to Gly/Gly homozygotes, bearers of the Trp allele for the Gly460Trp (rs4961) polymorphism in the ADD1 gene demonstrated a lower baseline plasma renin activity and a superior antihypertensive response to hydrochlorothiazide therapy. According to several studies, rs4961 polymorphism alters ion transport across the cell membrane, potentially modulating renal sodium handling.

Another gene GNB3 has been evaluated for hydrochlorothiazide responses, which encodes the β3-subunit of the G-protein (2). According to a study, the GNB3 gene's T allele for the C825T (rs5443) polymorphism is connected to an RNA splice variant that lacks the exon 9 nucleotides 498–620, resulting in structural modifications in the β3-subunit of G-protein and potentially affecting signal transduction whereas, the T allele for this polymorphism was associated with better antihypertensive responses to hydrochlorothiazide with a gene-dose effect which was confirmed by the results of a study by Turner ST et al (12,13).

Another possible gene for reactions to hydrochlorothiazide is NEDD4L. The distal nephron's ability to reabsorb sodium is impacted by the ubiquitin ligase that this gene produces because it targets the epithelial sodium channel for destruction. Studies have demonstrated that NEDD4L gene polymorphisms alter plasma renin concentration, salt sensitivity, and susceptibility to hypertension, which is consistent with the gene's function.

Another strong and replicated signal associated with DBP response to HCTZ treatment in white subjects is the SNP rs16960228 near PRKCA. A genome-wide significant result was found in a meta-analysis combining the results from independent white hypertensive populations in Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR), Genetic Epidemiology of Responses to Antihypertensive (GERA), Nordic Diltiazem Study (NORDIL) and Genetics of Drug Responsiveness in Essential Hypertension Study (GENRES). The A allele was a significant predictor of greater DBP response to HCTZ. In addition, this study showed functional evidence that the A allele was associated with higher pretreatment PRKCA expression in white PEAR participants.

β-Blockers

β-Blockers are not considered the first line of treatment, but still, they are commonly prescribed to control hypertension as it controls the heart rate and cardiac output. Antihypertensive drugs cause the blocking of the kidney's juxtaglomerular cells, which lowers renin secretion and, in turn, lowers the amount of circulating angiotensin II produced.

The β1-adrenergic receptor, which is encoded by the protein ADRB1, is the main protein target of all -blockers. This gene contains two frequent and well-studied genetic polymorphisms that alter the encoded amino acids: rs1801252, which results in a serine-to-glycine change at the

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position of the protein (Ser49Gly), and rs1801253, which causes an arginine-to-glycine change at the position 389 of the protein, (Arg389Gly). When these two polymorphisms disrupt intracellular signaling mediated by the β1-adrenergic receptor, they provide significant evidence for functional impact (14).

Calcium Channel Blockers

Calcium Channel Blockers are heterogeneous type of drug which are commonly used to treat cardiovascular conditions, including hypertension. 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. The responses to CCB's antihypertensive effects or the risk of unfavorable cardiovascular outcomes are influenced by polymorphisms in the genes encoding various ion channels, including the voltage-gated calcium channels α1C (CACNA1C), α1D (CACNA1D), and β2 (CACNB2), the large-conductance calcium and voltage-dependent potassium channel β1 (KCNMB1), and the ERG potassium channel (KCNH2). Calcium channel blockers are largely metabolized in the liver via the cytochrome P450 3A5 (CYP3A5) (15).

Angiotensin II Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors

The modulator of blood pressure and sodium homeostasis is a renin-angiotensin system. Through interconnected mechanisms in the kidney, central nervous system, and cardiovascular system, these effects are synchronized. Angiotensinogen is converted by the renin-angiotensin system into angiotensin I, which is then further cleaved by the angiotensin-converting enzyme (ACE) to create angiotensin II, the system's final effector, to generate the physiologic effects of the renin-angiotensin system. ACE inhibitors, which prevent the synthesis of angiotensin II, and angiotensin II receptor blockers (ARB), which bind to AT1R and counteract the effects of angiotensin II, are two different kinds of medications that target the renin-angiotensin system. For a pharmacogenomic approach to these medications, genes encoding parts of the renin-angiotensin system are the most plausible candidate genes. AGT and CYP11b2 are two genes that are a part of the renin-angiotensin system's classical cascade and may therefore influence how well ACE inhibitors and ARB work to lower blood pressure. Angiotensinogen is produced by the AGT gene, and the SNP Met235Thr (rs699), which causes a threonine to replace a methionine in codon 235 of the protein, is the most researched polymorphism of this gene. There is no agreement on the impact of this polymorphism on the antihypertensive responses to ACE inhibitors or ARB, similar to the I/D polymorphism in the ACE gene (16).

Antihypertensive pharmacokinetic interactions on genetic polymorphisms

Drug metabolizing enzymes

The drug-metabolizing enzymes are primarily expressed in the liver but are also expressed in small quantities in the small intestine, lungs, placenta, and kidneys. The microsomal enzyme used in drug-metabolizing enzyme are cytochrome P450 (CYP). The Pharmacogene Variation Consortium (Pharm Var) has documented over 100 allelic and sub-variants of the CYP2D6 gene.

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The CYP2D6 gene's allelic variations and subvariants can be used to explain a person's therapeutic medication response, side effects, and tolerance.

Drug transporters

Drug transporters are significant factors in the absorption, distribution, and elimination of many drugs, whereas any genetic alterations of drug transporters may cause particular differences in pharmacokinetics or pharmacodynamic characteristics. Like P-glycoprotein (P-gp) drug transporters determine the range of drugs that have to be uptake and efflux from or into the lumen. The P-gp drug efflux pump is encoded by the ATP-binding cassette subfamily B member 1 (ABCB1) or MDR1 gene, whose genetic variability affects interindividual variations in bioavailability. Amlodipine's hypotensive impact on hypertensive patients (patients achieved target BP, 140/90 mmHg) was linked to the MDR1 or ABCB1 gene rs1045642 TT genotype.

Although there have been several attempts to study the function of genetic variations linked with antihypertensive drug response, there is presently no pharmacogenetic test that can be used to direct the treatment of hypertension in clinical practice. The absence of solid information about the impact of genetic variations on the enhancement of antihypertensive response presents a barrier in the clinical application of a genetically guided prescription. Firstly, the association results are frequently not replicated in populations from different ethnicities, races and geographic regions. It should be noted that these different populations must not be necessarily of a different racial/ethnic group. In hypertension pharmacogenetics, the majority of association findings are most likely due to tagging SNPs rather than functional variants, which may not replicate across different racial/ethnic groups. This would be due to the differential patterns of linkage disequilibrium, which could account for the non-replication of the associated tagging SNPs. Secondly, for pharmacogenetics to be adopted in clinical practice, detailed instructions on how to use genetic information to modify drug regimens are required, followed by in-depth training for healthcare practitioners. The Pharmacogenomics Knowledge Base (PharmGKB) is a resource that compiles information about human genetic variation on drug responses to support personalized medicine projects. Moreover, PharmGKB and the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network aim to provide peer-reviewed guidelines based on the quality of the evidence and the strength of the recommendation to facilitate the translation of pharmacogenomic findings to clinical decision.

Future aspects of pharmacogenetics in the Treatment of Hypertension

Investigating interactions between polymorphisms from other genes within drug response pathways is another promising method to get around the restrictions of hypertension pharmacogenomics, in addition to enhancing methods that concentrate on single locus analysis. A single locus may not be the appropriate clinical target for every person, given the polygenic character of hypertension. Given that these ideas are relatively new in the pharmacogenomics of hypertension, further studies in different populations are required to replicate the findings

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reported by the studies presented here. Utilizing a genetic risk score is another method that considers the polygenic character of hypertension (GRS). Recently, a method was created to assess the effects of several blood pressure-related variations on blood pressure readings, the risk of hypertension, and other cardiovascular disorders. It's interesting to note that GRS analysis revealed that the sum of all blood pressure-rising alleles might raise systolic blood pressure by 10 mm Hg and raise the risk of cardiovascular events. Therefore, using this approach in the next investigations on the pharmacogenomics of hypertension looks fascinating.

Discussion

There are various drugs that are recommended by ACC/AHA for the management of hypertension. The protocol is approached, with interindividual variability between patients in response to drugs or experiencing adverse effects because of the complex trait of blood pressure. Our understanding of the genetic regulation of blood pressure has increased as a result of genome-wide association studies (GWAS), which have helped to find numerous novel loci implicated in blood pressure regulation (10,12). Findings from GWAS are also useful in identifying hypertension risk and choosing the best course of treatment. Human genome sequencing attempts to identify and comprehend the pathology of a disease, as well as to aid in the development of novel strategies for enhancing therapeutic efficacy and reducing side effects for a given patient. Pharmacogenetics investigations are currently receiving more attention from researchers in India (13,14). But because hypertension is a complicated medical illness, research on its pharmacogenetics frequently yields contradictory and inconsistent findings concerning BP response, genetic polymorphisms, and the usage of antihypertensive drugs. Pharmacogenetic testing faces challenges that must be overcome for us to have a consistent approach when interpreting and using the results of genetic tests. For this reason, evidence-based practice resources are necessary. Therefore, improving blood pressure control and reducing cardiovascular risk this would improve the quality, safety, and effectiveness of patient care (8,9).

In the recent scenario, pharmacodynamic mechanism gains more popularity. Drug responses depend upon specific molecular receptors like the *NEDD4 L* gene and *ADD1* gene regulate the homeostasis of sodium balance in the renal tubule. In patients with NEDD4 L and ADD1 gene variations, hydrochlorothiazide reduces sodium reabsorption in the renal tubule, indicating a reduction in blood pressure. Downregulation of the β_1 receptor by the *ADRB1* gene variant increases the risk of hypertension, and GKR4 gene variation leads to treatment failure (17,18).

The influencing genetic polymorphism is affected by the pharmacokinetic mechanism of a drug. Study by Gaedigk A et al. stated that there was variability in the allele distribution and these individuals could be categorized as ultra-rapid, extensive, intermediate, and poor metabolizers (19).

Moreover, hypertension is a complex medical condition, hypertension pharmacogenetics may give conflating results regarding genetic polymorphisms, BP response, and the use of

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antihypertensive drugs. However, the transfer of important genetic information from the bench to the clinic is quite difficult. While pharmacogenetics testing has made inroads in oncology, cancer is a situation where drug efficacy may have an immediate impact on short-term survival and drug toxicity may be extremely severe (2). Given the variety of medication alternatives available, primary care physicians who treat the majority of HTN are likely to be very passive and continue managing BP through trial and error. Many modern doctors received their medical education before it was feasible to sequence with the human genome, and their degree of comfort with understanding and applying pharmacogenomic data to determine the best course of therapy for their patients may differ significantly. Clinical HTN specialists at academic medical facilities could be more likely to be the first group of doctors to use pharmacogenomic data provided by a clinical decision support system. It would be highly beneficial to use a streamlined pharmacogenomic method to place hypertension patients on the most effective, efficient, and well-tolerated medication regimen. This would mean fewer visits from patients to modify their blood pressure medications, fewer prescriptions per patient, and perhaps even improved adherence to their treatment plan. Less cardiovascular and renal problems, as well as an improvement in quality of life and lifespan for our hypertensive patients, would result from better blood pressure management. Presenting the improved outcomes in clinical trials would be a powerful stimulus to bring pharmacogenomics into clinical use in patients with HTN and fulfill the promise of personalized medicine (19,20).

Conclusion

The most recent pharmacogenomic literatures have been reviewed in this article for the five main groups of antihypertensive drugs now prescribed: diuretics, β-blockers, ACE inhibitors, ARBs, and CCBs. While many studies show that genetic variants have a major impact on how blood pressure responds to antihypertensive drugs, several studies have been unable to identify any meaningful effects or confirm prior findings. These discrepancies could be caused by interethnic variations in the distributions of the polymorphisms that were tested or detected, or by epigenetic changes that could conceal the role of DNA sequence variants. Additionally, the inconsistent results could be explained by heterogeneous phenotypes. In this instance, variation in the etiology and mechanisms at play may explain the variations in reported phenotype, decreasing the likelihood that connections between genetic variants and antihypertensive responses will be successfully discovered. Therefore, it is crucial to carefully phenotype subjects, and it may also be necessary to look at illness surrogate indicators.

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