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Has pharmacogenetics brought us closer to “personalized medicine” for initial drug treatment of hypertension?

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Abstract

Purpose of review—To describe recent advances in antihypertensive pharmacogenetics and discuss challenges related to translating this knowledge into “personalized medicine” for the initial drug treatment of hypertension.

Recent findings—Recent studies included both prospective and retrospective analyses ranging from small clinical investigations of 42 participants to large, multicenter, randomized, outcome-based clinical trials of nearly 40,000 subjects. Treatment with drugs from five classes of antihypertensives was evaluated in these studies. The duration of treatment ranged from weeks-long follow up for BP response to a decade long follow up for clinical outcomes. In total, associations with 12 different candidate genes were assessed. These studies present the now familiar mix of significant and nonsignificant pharmacogenetic findings that are sometimes consistent with, sometimes inconsistent with, previous findings in antihypertensive pharmacogenetics.

Summary—Recent research in antihypertensive pharmacogenetics has added to the existing evidence base, and novel genes and variants as well as new methodologies are cause for continued optimism. However, translation of genomic science to clinical settings has not kept pace with growing interest in personalized medicine for hypertension. New research paradigms may be needed to translate pharmacogenetics into clinical tools. Clinical application will also require a trained clinical workforce, validated genetic tests, and payors willing to fund pre-treatment testing.

Keywords

antihypertensive pharmacogenetics; personalized medicine; genes; hypertension

Introduction

Worldwide, hypertension affects 972 million persons, including nearly 1 in 3 US adults [1, 2]. Of the approximately 60.3 million Americans being treated for hypertension, about 21 million cases remain uncontrolled [1]. Since evidence suggests that blood pressure (BP) response and outcomes associated with antihypertensive drugs are influenced by genetic variation, there is much interest in developing pharmacogenetic tools to help clinicians better predict which treatments will benefit patients based on their genetic profile. Many pharmacogenetic studies of hypertension treatment have been conducted with mixed results. In this paper we review the recent findings for pharmacogenetic studies of antihypertensive

treatment, and seek to answer the question: Has pharmacogenetics brought us closer to “personalized medicine” for initial drug treatment of hypertension?

Current state of knowledge for the pharmacogenetics of hypertension

We restricted our review of recent research to antihypertensive pharmacogenetic studies published during approximately the previous year. Table 1 summarizes the ten studies reviewed, and features of study design, drug treatment, and outcomes or phenotypes assessed. Studies included both prospective and retrospective analyses ranging from small clinical investigations of 42 participants to large, multicenter, randomized outcome-based clinical trials of nearly 40,000 subjects. Treatment with drugs from five different classes of antihypertensive agents was evaluated in these studies. The duration of treatment exposure ranged from weeks-long follow up for BP response to a decade-long follow up for clinical cardiovascular outcomes. All prospective studies reported in the past year involved participants with pre-existing hypertension or a history of a cardiovascular event. In total, associations with 12 different candidate genes were assessed, most of which have been previously considered in a pharmacogenetic context. One study examined whether specific combinations of variants from three genes interacted with treatment and were associated with differential BP lowering. Only two studies included haplotype analyses (i.e., a combination of variants at multiple loci that are transmitted together on the same chromosome). One study reported the finding of a modest sized (389 participants, 100 K single-nucleotide polymorphisms) genome-wide association study (GWAS). Table 2 summarizes the findings of these studies, arranged by gene and variant.

Renin-angiotensin-aldosterone system genes

Variation in the *ACE* (angiotensin converting enzyme), *AGT* (angiotensinogen), *AGTR1* (angiotensin receptor 1), and *CYP11B2* (cytochrome P450, subfamily XIB, polypeptide 2) genes have been assessed in relation to a variety of antihypertensive treatments and several outcome measures. Two recent studies investigated the ACE insertion-deletion (ID) variant, one with respect to BP response [3], the other to stroke and myocardial infarction (MI) [11]. Neither study reported significant pharmacogenetic associations with ACE inhibitor treatment. The clinical outcome findings were consistent with a previous study done with lisinopril [13]; however, a previous BP-response study did report significant associations between fosinopril and ACE (ID) [14]. Variants (–6 A/G and A1166C) in the AGT gene have been evaluated in relation to BP response, and no significant pharmacogenetic associations were reported [3, 4]. Although there are no previous studies of the –6 A/G variant in this context, previous studies of the A1166C polymorphism with various treatments have been inconsistent and of dubious comparability [15, 16]. Four recent studies evaluated pharmacogenetic associations with variants of the AGTR1 gene. Variant C573T interacted with ACE inhibitor treatment: C allele carriers had reduced risk of MI with treatment compared to TT homozygotes [11]. The AGTR1 C573T polymorphism has not previously been studied in this specific context. In individuals homozygous for the T allele of the AGTR1 C5245T variant, plasma irbesartan concentration was related to the change in systolic BP (SBP); this was not the case for other genotypes [6]. This polymorphism has not previously been studied in a comparable context. Finally, a variant of CYP11B2, a gene encoding a steroid necessary for the synthesis of aldosterone, was found not to interact with fosinopril treatment in BP response to the drug [3]. This variant has not previously been studied in this context. In summary, we find that genes that have been reported more extensively (*ACE* and *AGT*) yielded null associations, while the newer genes (*AGTR1* and *CYP11B2*) yielded significant findings.

Sympathetic nervous system/vascular tone genes

In contrast to the renin-angiotensin-aldosterone system, pharmacogenetic findings are more promising for genes that regulate vascular tone. Lemaitre et al.'s study of beta-blockers and MI and ischemic stroke assessed the pharmacogenetic role of individual polymorphisms and haplotypes of *ADRB1* (beta-1-adrenergic receptor) and *ADRB2* (beta-2-adrenergic receptor) [7]. None of the five SNPs, or haplotypes constructed from these SNPs, in *ADRB2* was associated with the outcomes. However, two of the seven SNPs in *ADRB1* (rs17875422, rs2429511) interacted with treatment and yielded differential MI and stroke risks. Previous studies of *ADRB1* reported significant interaction between variants tested here and beta-blocker treatment for BP-lowering [17, 18]. For *ADRB2*, the Lemaitre et al. findings are consistent with (although not entirely comparable to) previous observations [19]. Pacanowski and colleagues investigated *ADRB1* and *ADRB2* haplotypes in a study of atenolol and verapamil's effect on death, nonfatal MI, and nonfatal stroke risk. They found death rates were significantly higher in individuals with the *ADRB1* Ser49-Arg389 haplotype in patients assigned to verapamil but not those assigned to atenolol [10]. These Ser49-Arg389 haplotype findings are consistent with previous beta-blocker studies [17, 20–22], although between-study comparisons are challenging because of differing washout and treatment protocols. In their analysis of 2594 individuals without a history of cardiovascular disease, Kelley-Hedgpeeth et al. found that the Lys65 allele of the *KCNMB1* (potassium channel, calcium-activated, large conductance, subfamily M, beta member 1) Glu65Lys variant was associated with greater BP lowering with beta-blocker treatment than Glu65 homozygotes [5]. *KCNMB1* is responsible for the smooth muscle tone and neuronal excitability through its effect on conductance, voltage and calcium-sensitive potassium channels. Comparisons with other studies of the *KCNMB1* gene are difficult because information on previous antihypertensive treatment and washout protocols for these studies differs or is incomplete.

Ion transport and fluid balance

Genes regulating ion transport and fluid balance may hold promise for pharmacogenetic studies, and 4 different genes contributing to ion transport and fluid balance have been reported in hypertension pharmacogenetic studies in the past year. The *ADD1* (adducin 1) Gly460Trp variant has been associated with BP response to the diuretic, hydrochlorothiazide (HCTZ) [23]. In a case-control study of HCTZ, *ADD1* Gly460Trp, and BP response, Manunta and colleagues found Trp allele carriers had significantly greater BP reduction with HCTZ than GlyGly individuals [9]. Manunta et al. also examined single-variant associations of *NEDD4L* (ubiquitin protein ligase *NEDD4*-like) (rs4149601) and *WNK1* (protein kinase, lysine-deficient 1) (5 SNPs) in this study and found no pharmacogenetic associations. In a novel analysis, these authors also evaluated the associations of combinations of these gene variants. When considered together, there was a significant trend in decreases of SBP for different combinations of genotypes. Using data from the largest pharmacogenetic study to date, two variants of *NPPA* (natriuretic peptide precursor A) were examined in a randomized comparative study of chlorthalidone, doxazosin, amlodipine, and lisinopril for 6-month BP response and long-term (4.9 year) cardiovascular outcomes. Although no pharmacogenetic associations were found for the G664A variant, there was evidence of a pharmacogenetic association of the T2238C polymorphism. Minor C allele carriers had more favorable outcomes (coronary heart disease (CHD), stroke, all-cause mortality, and combined CHD and CVD events) when randomized to chlorthalidone whereas TT individuals had more favorable outcomes when randomized to amlodipine. A similar effect was reported for 6-month blood pressure response: Relative to the common TT genotype, the minor C allele carriers had more significant reductions in blood pressure when randomized to chlorthalidone versus the other treatment groups [8].

Other genes

In their genome-wide association study and validation, Turner et al. found that SNPs and haplotypes in *LYZ* (lysozyme) and *YEATS4* (yeats domain-containing protein 4) were associated with diastolic BP response to HCTZ [12]. Although these genes have not been previously studied in this context, the authors suggest their findings may be consistent with a gene expression profiling study [24].

Summary of recent research

The studies reviewed here present the now familiar “mixed bag” of significant and nonsignificant pharmacogenetic findings that are sometimes consistent with, and sometimes inconsistent with, previous findings in antihypertensive genetics research. That said, we note that a number of the more newly investigated genes (e.g., *CYP11B2*, *AGT1R*) hold promise. However, the mixed results associated with the more studied genes (and our optimism regarding less familiar genes and variants) may exemplify what has been called the “winner’s curse” in genetic epidemiology [25]: candidates such as *ACE* and *AGT* should not be dismissed, and subsequent studies of genes such as *AGT1R* and *CYP11B2* must be conservatively powered to assess their actual potential. We also note that our conservative approach in comparing recent to older studies resulted in many claims that valid comparisons among studies were tenuous or simply not valid. This situation presents a challenge to researchers: the many dimensions by which ostensibly similar studies can differ from each other (population characteristics, washout period, drug class, drug formulation, treatment duration, phenotype definition and measurement, etc.) could conceivably account for differences in findings. This fact suggests that greater coordination and collaboration in the design and implementation of pharmacogenetic studies could increase the likelihood of valid comparisons and fruitful meta-analyses. Of course, differences among studies—when consciously implemented and carefully considered when making comparisons—could also be leveraged to increase our knowledge of gene-environment interactions. Finally, a number of methodological approaches exemplified by these recent studies—specifically the multigene analysis by Manunta et al. and the GWAS by Turner et al.—offer new research/analytical paradigms that have tremendous potential to advance the field.

How prepared are clinicians for personalized hypertension treatment?

Although a sound scientific evidence base is a necessary criterion for the establishment of clinically efficacious antihypertensive pharmacogenetics, it is by no means sufficient. Successful and routine application of genetic information in clinical practice will require clinicians to embrace a new paradigm. Pre-prescription genotyping has taken hold in practice to a limited extent for other conditions. For example, *CYP450* (cytochrome P450) gene variants can be typed to determine the most effective dose of serotonin reuptake inhibitors [26]. A recent study showed that pharmacogenetic tests may be useful in initial warfarin dosing: using genetic information from *CYP2C9* (cytochrome P450, subfamily IIC, polypeptide 9) and *VKORC1* (vitamin K epoxide reductase complex, subunit 1) variants to formulate a dosing algorithm improved the estimation of the appropriate initial dose of warfarin over using a clinical algorithm alone [27]. At least one professional organization has endorsed the use of this genetic test in certain clinical situations [28]. Importantly, current research is also focusing on whether or not there is evidence that this testing has improved clinical outcomes for patients compared to usual care.

Physicians wishing to incorporate pre-prescription pharmacogenetic testing into their practice must be willing to include the extra logistical steps of submitting lab samples for analysis and waiting for the results before initiating hypertension treatment. Unlike the

vanguard genetic tests mentioned above, however, the complexity of hypertension and its sequelae will necessarily lead to a more complex treatment models than single gene variants informing decisions about dosing of a single treatment. If or when the time comes that genetic testing can provide useful guidance on initial treatment of hypertension, clinicians will be required to be knowledgeable regarding appropriate interpretation of genetic tests. This may prove to be challenging since the physician workforce—by its own admission—is not adequately trained in genetics [29]. Additional complexity will result in hypertension pharmacogenetics since any screening test will likely be composed of (i) a panel of genes rather than a single one, given the redundancy of gene pathways that regulate BP; (ii) multiple clinical outcomes (including, but not limited to, BP lowering, myocardial infarction, stroke, and renal failure); and (iii) a variety of drug classes and individual drugs within a class. The challenge will be to develop tools to help clinicians use a complex model quickly and effectively to inform their treatment decisions for hypertension to provide the best care possible for their patients. These tools will most likely take the form of an information “matrix” that shows risks of a variety of outcomes for a variety of treatments for a panel of gene variants. Rather than a “one size fits all” pharmacogenetic recommendation (which would be antithetical to the very idea of personalized medicine), a patient’s individual risk for a variety of potential outcomes (stroke, myocardial infarction, heart failure, etc.) might also need to be taken into account. Ultimately, successful application of pharmacogenetic tests for hypertension by family medicine specialists and internists—the clinicians most often diagnosing and treating hypertension—will depend on the ease of integrating and interpreting genetic data along with more traditional diagnostic data. Mechanisms for communicating this information and the decision process will also need to be developed and tested.

How prepared is the public for personalized HTN testing/treatment?

Two European studies conducted in the past few years looked at both patients’ and healthcare professionals’ viewpoints on pharmacogenetic testing, and report generally positive expectations regarding the potential benefits of testing by patients, particularly with regard to personalizing drug doses and minimizing side effects of drugs [30, 31]. Some patients, however, raised concerns about stress and anxiety related to the tests, as well as the potential violation of privacy. Patients also voiced their expectation that pharmacogenetic services be provided by professionals who can confidently interpret, explain, and effectively utilize the results. For personalized medicine to become a reality for the initial treatment of hypertension, patients must have a positive perception of the risk-benefit ratio. Direct-to-consumer genetic testing is increasingly available without any involvement of a health care practitioner; these services provide individuals with their genotype information and an assessment of their risk of a variety of conditions. If this industry grows, one effect may be that individuals will begin to see their genetic information as a potential tool that can be used to optimize treatment, making them more comfortable with idea of pharmacogenetics.

What are the ethical, legal, social issues associated with hypertension pharmacogenetics?

Because genetic testing in general is fraught with ethical, legal and social concerns, including privacy issues, the psychological impact of learning about genetic susceptibilities, and implications for family members, caution must be exercised in the development of pharmacogenetic tools. However, it may be useful when examining these topics to distinguish between genetic tests for the purpose of assessing general risk of disease and pharmacogenetic tests which are used as a tool to help guide treatment decisions. For example, testing for risk of an adult-onset disease such as cancer in the absence of any symptoms puts an individual in the difficult position of making decisions about their future

health over the long term without knowing for certain whether they will ultimately develop the disease or not. In contrast, hypertension pharmacogenetic testing will be used after hypertension has been diagnosed to present patients with a more focused “single point in time” decision regarding treatment options. Therefore, while not free from ethical, legal and social concerns, the implications of pharmacogenetic testing differ from the implications for testing for disease susceptibility.

What needs to be done to move hypertension pharmacogenetics into translation to personalized medicine?

For hypertension pharmacogenetics to be translated into clinical practice, an evidence base must be established. However, creating an evidence base wherein we set the evidence bar either too low or too high will negatively affect the future of antihypertensive pharmacogenetics. Khoury et al. recently published a paper weighing the ramifications of both excessively high and excessively low evidence thresholds for moving genetic research into clinical practice, suggesting a need for the establishment of a “flexible and sustainable process for translational research and evaluation of promising genomic applications...” [32]. Khoury has also described 4 “phases” of genomics translational research: Phase 1 research seeks to move basic genetic knowledge into a candidate genetic test and associated intervention; Phase 2 research begins initial assessments of the validity and utility of the genetic test/intervention and stimulates development of evidence-based guidelines for the clinical use of the test/intervention; Phase 3 research seeks to move the evidence-based guidelines into clinical practice through delivery, dissemination, and diffusion research; Phase 4 research evaluates the real-world health outcomes of the genetic test/intervention in clinical practice [33]. According to Khoury, the vast majority of research in genomic medicine so far has been limited to Phase 1 level. Although this traditional model of gathering evidence has well-served the field of evidence-based medicine, the development of a pharmacogenetic evidence base and translation of genetic findings into clinical practice may benefit from a less linear approach. For example, one option might be to translate a full panel of genetic data (i.e., multiple genes and variants) from a current pharmacogenetic study population into a working model to predict treatment-dependent outcomes and then test the model in a small pilot study designed to mimic “real-world” use of the genetic and intervention test in a clinical setting. Clinicians could be trained in the use of a “prototype” pharmacogenetic test using a panel of genes. Participants could then be assigned to first-line treatment based on the working gene/treatment model, with Phase 2-, 3-, and 4-type follow-up research being undertaken simultaneously. This could provide the kind of “feedback loops to allow integration of new knowledge,” which Khoury et al. describe.

Conclusion

The recent research in antihypertensive pharmacogenetics has added to the existing evidence base, and novel genes and variants, as well as new methodologies, are cause for continued optimism. However, translation of genomic science to the clinical setting has not kept pace with growing interest in personalized medicine for hypertension. The current paradigm, which relies on uncovering pharmacogenetic associations on a gene variant-by-gene variant basis, and subsequently replicating findings, is proving to be a slow, difficult and expensive process, since each particular variant is likely to contribute small effects on complex conditions like hypertension. A new paradigm, perhaps a more “global” look at candidate genes to create a panel of key variants which together can better predict treatment-dependent outcomes, may be needed to translate pharmacogenetics into tools for clinical practice. Finally, clinical application will require a trained clinical workforce, valid genetic tests, and payors willing to fund pre-treatment testing.

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Table 1

Designs of recent antihypertensive pharmacogenetic studies.

First Author	Phenotype	Treatment	Design
Filigheddu [3]	BP at 4 wk	fosinopril	Prospective; 191 with HTN.
Gluszek [7]	BP, ambulatory MAP at 8 wk	perindopril	Prospective; 64 with HTN.
Kelley-Hedgepeth [33]	BP	BB, CCB, diuretic, RASB (as classes)	Post hoc; 2594 without CVD.
Kurland [10]	BP at 12 wk	irbesartan	Prospective; 42 with HTN and LVH
Lemaitre [11]	MI, ischemic stroke	BB (as class)	Retrospective; 938 cases with MI or stroke, 2249 controls.
Lynch [21]	CHD, stroke, all-cause death, combined CVD outcomes for 4.9 yr follow up; BP at 6 mo	chlorthalidone, doxazosin, amlodipine, lisinopril	Post hoc analysis of a randomized clinical trial (ALLHAT); 38,462 with HTN & 1 CVD risk factor.
Manunta [20]	BP at 4 wk	HCTZ	Prospective; 195 cases with high DBP, 195 controls with low DBP.
Pacanowski [15]	Death, nonfatal MI, nonfatal stroke for 2.8 yr follow up	atenolol, verapamil	Post hoc analysis of a randomized clinical trial (INVEST); 5895 with CAD.
Schelleman [4]	MI, stroke for 10 yr (max) follow up	ACEI, BB (as classes)	Prospective cohort; 4097 with HTN.
Turner [22]	DBP at 4 wk	HCTZ	Case-control GWAS and follow-up. 194 blacks, 195 whites with HTN from opposite tertiles of DBP response to drug.

ACEI, angiotensin converting enzyme inhibitor; BB, beta blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GWAS, genome-wide association study; HCTZ, hydrochlorothiazide diuretic; HTN, hypertension; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MI, myocardial infarction; RASB, rennin-angiotensin system blocker

Table 2

Findings of recent antihypertensive pharmacogenetic studies.

Gene, Variant(s)	Finding	Ref
<i>Single Variant Associations</i>		
ACE, ID	No associations *	[4]
ACE, ID	No associations	[3]
ADD1, Gly460Trp	T carriers had significantly greater BP reduction with HCTZ than GG individuals.	[20]
ADRB1, 7 SNPs	2 SNPs (rs17875422, rs2429511) in ADRB1 interacted with BB treatment for MI and stroke risk.	[11]
ADRB2, 5 SNPs	No associations	[11]
AGT, -6 A/G	No associations	[3]
AGTR1, C573T	MI risk with ACEI treatment reduced for AGTR1 C allele carriers. No associations for stroke with either ACEI or BB.	[4]
AGTR1, A1166C	No associations	[7]
AGTR1, A1166C	No associations	[3]
AGTR1, C5245T	Plasma concentration of irbesartan was related to the change in SBP in TT individuals but not for other genotypes	[10]
CYP11B2, -344 C/T	No associations	[3]
KCNMB1, Glu65Lys	BB treatment may be responsible for lower BP in Lys65 allele carriers.	[33]
NEDD4L, rs4149601	No associations	[20]
NPPA, T2238C	Minor C allele carriers had more favorable CVD outcomes with chlorthalidone; TT individuals had more favorable outcomes with amlodipine.	[21]
NPPA, G664A	No associations	[21]
WNK1, 5 SNPs	No associations	[20]
<i>Variant combinations, haplotypes, and GWAS findings</i>		
ADD1, NEDD4L, WNK1, Combinations of 7 variants	Individuals with specific combinations of variants had significantly more SBP-lowering than other combinations.	[20]
ADRB1, Ser49Gly-Arg389Gly haplotypes	Ser49-Arg389 haplotype carriers had higher death rates in verapamil but not atenolol group.	[15]
ADRB1, 7-SNP haplotypes	No pharmacogenetic associations	[11]
ADRB2, Gln27Glu-Arg16Gly-Arg175Arg haplotypes	No associations	[15]
ADRB2, 5-SNP haplotypes	No associations	[11]
GWAS, 100K SNPs	SNPs and haplotypes in LYZ and YEATS4 were associated with DBP response to HCTZ.	[22]

* "No associations" signifies no significant evidence of gene variant x drug treatment interaction.

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; GWAS, genome-wide association study; HCTZ, hydrochlorothiazide diuretic; MI, myocardial infarction; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism