 doi:10.20944/preprints201905.0035.v1

Review

Pharmacogenomics in hypertension: Where we stand today

Patrick N. Cunningham [1,*] and Arlene B. Chapman [1]

[1] Section of Nephrology, University of Chicago, Chicago, IL 60637, USA
* Correspondence: pcunning@medicine.bsd.uchicago.edu

Abstract: Hypertension is a common and growing medical problem that leads to enormous cardiovascular and kidney disease worldwide. While many drugs exist to treat hypertension, there is large individual variation in how a given individual may respond to different agents, which contributes to dismal rates of hypertension control. While demographic factors predict which drugs may work better in certain individuals, a great degree of this variation has a genetic basis. In recent years, genome wide association studies have begun to identify specific gene variants that predict drug response to particular agents. This review identifies the major genetic variants influencing antihypertensive response that have emerged from this growing body of work. For novel genetic variants without a previously known biologic basis in blood pressure, it is crucial to validate initial findings in subsequent studies. This information may eventually lead to a more personalized approach to hypertension management that will improve blood pressure control and patient outcomes. The integration of this large amount of data and its real world application will be highly challenging, but strategies to accomplish this are discussed.

Keywords: blood pressure, diuretics, thiazide, beta blocker, calcium channel blocker, renin angiotensin system

 doi:10.20944/preprints201905.0035.v1

Introduction

Hypertension (HTN) is responsible for significant morbidity and mortality across the United States, and indeed, worldwide. As the prevalence of obesity increases, the disease burden of hypertension will only increase [1]. The underlying pathophysiology of hypertension is complex and varies significantly between patients, which makes HTN challenging to treat successfully. There are multiple choices of drugs and drug classes to treat hypertension, and yet the rate of successful blood pressure control is disappointing, typically less than 50%, due in part to great variability between patients as to which drugs are effective. Choices of what antihypertensive class to choose can be guided partially by demographic factors, with diuretics and calcium channel blockers generally more effective in African Americans and the elderly, and beta blockers and drugs targeting the renin-angiotensin system (RAS) more effective in Caucasian and younger patients [2]. Nevertheless agents are often selected in a trial and error fashion. The hit-or-miss nature of this approach is inherently inefficient and contributes to greater medical costs, delayed BP goal attainment, poorer BP management success rates, and continued high cardiovascular mortality. Predictive models or genetic information which could help identify those agents that would be most effective in a given patient would be of immense clinical value, improve BP control, and would undoubtedly reduce the consequences of hypertension and save medical costs.

Increasingly the field of pharmacogenomics has been used in areas such as cardiology and oncology to inform clinicians which drugs may have greater or lesser effectiveness as well as potentially greater risk profiles of adverse effects. The pathogenesis of elevated BP and HTN is a complex interplay of environmental and multiple genetic factors which may differ greatly between

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 May 2019 doi:10.20944/preprints201905.0035.v1

individuals. The genetic basis of HTN is based on both rare Mendelian regulation of BP as well as heritability estimates of BP in mono and dizygotic twins in shared environments demonstrating heritability of up to 50% [3]. Several autosomal recessive monogenic causes of HTN that have been identified, such as Gordon's syndrome, which results from mutations in the WNK kinase genes, leading to increased renal sodium reabsorption, and Liddle's syndrome, which is caused by mutations in genes *SCNN1B* or *SCNN1G* which lead to increased activity of the distal ENaC sodium channel, also leading to increased sodium retention by the kidney [4,5]. Additionally, a number of genetic causes of aldosterone excess or hypersensitivity to corticosteroids have been identified, such as mutations in *CYP11B2*, *CYP11B*, *HSD11B2*, and *KCNJ5* [6-9]. Although the individuals affected by these syndromes are often severely hypertensive, these single mutations with a Mendelian effect are extremely rare. The vast majority of patients with essential HTN have genetic contributions to their BP, but are more representative of a complex medical disorder where multiple gene variants which each have a small contribution to the BP phenotype [10], in the setting of interaction with environmental factors. There are likely hundreds of genetic variants which play a role, interacting with other variants that may be protective against hypertension.

One approach to identifying genetic variants associated with differential response to particular BP agents is to focus on the effect of candidate genes previously identified as having a mechanistic role in hypertension. This approach relies on prior knowledge of blood pressure regulatory systems and their genetic influences. Given that our knowledge of these systems is not complete and that there are other as of yet unknown regulators of each BP regulating system, significant bias is present in these types of studies, and both negative and positive findings can only be interpreted in a limited

 doi:10.20944/preprints201905.0035.v1

context. In contrast, a genome wide association study (GWAS) pharmacogenomic approach will identify completely novel SNPs which correlate with a greater or lesser response to specific BP agents. After the necessary statistical correction for the very large number of multiple comparisons of hundreds of thousands of SNPs tested in each patient using current gene arrays, no SNPs have emerged with an incontestable association with BP response to any antihypertensive agent ($p < 10^{-8}$). This is not surprising given the modest number of patients that can be studied in randomized trials, in contrast to the thousands of subjects analyzed in GWAS for incident HTN or other common diseases. However, multiple suggestive SNPs with p values in the 1×10^{-5} to 1×10^{-6} range have been identified in various studies. Regardless of the strength of the genetic associations, validation populations are needed to confirm candidate SNPs that have been identified. Such an unbiased approach using a GWAS of BP response to specific antihypertensive agents has successfully identified and validated clinically relevant variants that could not have been predicted based on our current understanding of the physiology of BP regulation [11-13]. In addition to cross-validation studies, as the cost of DNA sequencing technology has fallen significantly, multiple single studies have been performed describing associations of various SNPs, but either remain unvalidated, or subsequent validation attempts have failed to confirm an effect. This review will focus on gene variants in which the evidence for a significant effect on the response to antihypertensive agents is the strongest, which emerge from high quality, well powered studies with subsequent validation in separate cohorts. A summary of important hypertension cohorts used in these pharmacogenomics analyses is given in Table 1.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 May 2019 doi:10.20944/preprints201905.0035.v1

Table 1. Major hypertension pharmacogenomics studies

Study	Subjects (n)	Population	Drugs
NORDIL	3863	Norway, Sweden	HCTZ / atenolol / diltiazem
INVEST	5598	American - multiethnic	Atenolol / verapamil
PEAR1	768	European Americans, African Americans	HCTZ / atenolol
PEAR2	457	European Americans, African Americans	Chlorthalidone / metoprolol
GERA1	505	European Americans, African Americans	HCTZ
GENRES	228	Finland	HCTZ / bisoprolol / amlodipine / losartan
HCTZ-Milan	220	Italy	HCTZ
PHSS	465	Italy	HCTZ
LIFE	3503	Norway, Denmark, Finland	Atenolol / losartan
AASK	328	African Americans with chronic kidney disease	Metoprolol

[1]Abbreviations: NORdic DILtiazem Study; INternational VErapamil Trandolapril Study; INternational VErapamil Trandolapril Study; Pharmacogenomic Evaluation of Antihypertensive Responses 1; Pharmacogenomic Evaluation of Antihypertensive Responses 2; Genetic Epidemiology of Responses to Antihypertensives 1; GENes and Antihypertensive Drug RESponse; Milan Hypertension Pharmacogenomics of HCTZ; Pharmacogenomics of Hydrochlorothiazide Sardinian Study; Losartan Intervention For Endpoint reduction in Hypertension; African American Study of Kidney Disease and Hypertension

 doi:10.20944/preprints201905.0035.v1

Diuretics

Diuretics, usually of the thiazide class which targets the distal convoluted tubule, are one of the most common initial agents in treatment of HTN, and currently recommended as first line therapy by recent JNC 8 and ACC/AHH guidelines. Importantly, the BP response to this class of antihypertensive agents is quite uneven [2,14,15]. Much has recently been learned about the some key genetic influences on thiazide diuretic BP response, from both candidate driven and GWAS approaches. Variants in *NEDD4L* (neural precursor cell-expressed developmentally downregulated 4-like), were previously found to have a role in incident hypertension [16-18], and so emerged as an attractive candidate for pharmacogenomic study. NEDD4L controls the protein expression of the renal distal tubular sodium channel ENaC, as well as other sodium channels, through ubiquitination. Variation at the intronic SNP rs4149601 produces a cryptic slice site and leads to greater expression of ENaC and a hypertensive, low renin phenotype, which has been linked to increased cardiovascular mortality [19]. The NORDIL study (NORdic DILtiazem Study), whose participants were overwhelmingly Caucasian, found the carriers of the G allele to be associated with a greater decrease in SBP and DBP when treated with thiazide diuretics, but not CCBs, as would be expected [20]. This result was replicated by the PEAR1 study in a Caucasian population [21]. Additionally, carriers of the G allele were found to have better cardiovascular outcomes in the NORDIL population (OR 0.52, 95% CI 0.36-0.74) when treated with thiazides [20], and the INVEST cohort (INternational VErapamil Trandolapril Study) similarly found higher mortality in G allele carriers who were not treated with thiazides. The latter study also found that addition of a second SNP in the 5' untranslated region of *NEDD4*L, rs292449, improved the prediction model for SBP and DBP when analyzed as part of a haplotype with rs4149601. In summary, the clear biologic role of *NEDD4L*, the consistent findings

 doi:10.20944/preprints201905.0035.v1

of theses several studies, and the association with longer term outcomes in addition to short term BP response makes the pharmacogenomics implications of this gene very robust. It is worth noting however that these findings were from Caucasian populations and did not replicate in African Americans within the PEAR1 study (Pharmacogenomic Evaluation of Antihypertensive Responses 1), which is important given that hypertensive African Americans are more volume expanded and salt sensitive, with lower circulating plasma renin activity, and generally show more BP response to thiazide diuretics in comparison to Caucasians.

An example of pharmacogenomics markers of BP response in hypertensive African Americans was identified by an unbiased approach as opposed to a candidate gene approach shown by the association of three SNPS on the chromosome 12q5 region, rs317689, rs315135, and rs7297610, in the GERA1 study (Genetic Epidemiology of Responses to Antihypertensives 1). These SNPs are outside protein coding regions but in the vicinity of the genes for *LYZ* (lysosome), *FRS2*, and *YEATS4*. The strongest association was seen with rs7297610 near YEATS4, where the C allele correlated with greater BP response to HCTZ [22]. This finding was validated in hypertensive African American participants in a separate cohort from the PEAR1 study (SBP and DBP response -13.0 and -8.0 in the CC genotype, versus -9.6 and -5.2 mm Hg in the TT genotype). *YEATS4* had no previously known role in BP regulation, but it codes for the protein GAS41, a transcription factor which modifies gene expression through acetylation of histones H4 and H2A, and may participate in inflammatory signaling [23]. Support for a role in HTN and HCTZ response was strengthened by the subsequent finding that leukocytes in the CC variant participants had statistically greater *YEATS4* expression at baseline (p= 0.009) and a statistically greater decrease in expression (p=0.02) after HCTZ treatment,

 doi:10.20944/preprints201905.0035.v1

which was not observed in carriers of the T allele [11]. While the pathophysiology behind this mechanism has not been uncovered yet, the independent validation and changes in *YEATS4* expression level strengthen these findings; thus unexpected GWAS findings may eventually lead to a greater understanding in pathophysiology.

A separate unbiased analysis of a combined Caucasian cohort from the GERA1 and PEAR1 studies identified suggestive ($P < 1 \times 10^{-5}$) associations between BP response to thiazides in several SNPs, and then tested these candidates for replication in a larger cohort from the GENRES (GENes and Antihypertensive Drug RESponse), NORDIL, and the HCTZ-Milan (Milan Hypertension Pharmacogenomics of HCTZ) studies. Validation was found for two of these initially suggestive SNPs [13]. rs16960228 is located in an intron within *PKCA* (protein kinase Cα). Meta-analysis of these cohorts found a p value of 3.3×10^{-8}, which meets the commonly accepted threshold for genome wide significance testing of 10^{-8}. This variant had an opposite direction of effect for atenolol within the PEAR1 cohort, consistent with the partially opposing mechanisms of action of these two classes of drugs. Animal studies in *PKCA* knockout mice have recently shown BP differences attributable to altered vascular contractility [24]. Additionally, other SNPs in this gene were also found to correlate with DBP sensitivity to thiazides in an African American cohort of PEAR1. This same analysis also found that variation in rs2273359, located between genes *GNAS* (stimulatory G-protein α subunit) and *EDN3* (endothelin 3), correlated with SBP response to thiazides [13], with a p value of 5.5×10^{-8}. The region near *GNAS* is highly complex, involving several alternative promotors and variant transcripts, with animal work also suggesting a role in BP regulation and the adrenergic nervous system [25,26].

 doi:10.20944/preprints201905.0035.v1

A number of other reports have found gene variants associated with differential responses to thiazide diuretics, implicating variants in *TET2*, *CSMD1 [27]*, *GNB3 [28]*, and *VASP* (vasodilator associated phosphoprotein) [29]. While these variants have not been as consistently validated [30] and did not obtain p values < 10^{-8}, they do have biologic rationale as an aldosterone sensitive regulator of ENaC (*TET2*), a prior association with vascular disease and HTN (*CSMD1*), an association with HTN and renin levels (*GNB3*), or a prominent role in vascular biology (*VASP*). Studies showing variation at rs10995, downstream of *VASP*, were also interesting in that they not only predicted better blood pressure response in two independent cohorts, but also associated with the baseline level of *VASP* mRNA [29]. Thus the number of genes that may influence diuretic response is continuing to grow. As each genetic variant may have a relatively small influence, the challenge is to accurately integrate this information to get a more global idea of how an individual patient may respond to a certain antihypertensive drug class. An illustration of this is the combination of multiple data sets in a GWAS of HCTZ response in a combined cohort of over 1700 patients from the GENRES, GERA1, HCTZ-Milan, PHSS (Pharmacogenomics of Hydrochlorothiazide Sardinian Study), NORDIL, and PEAR1 studies. This meta-analysis did not find any Bonferroni-corrected variants of significance, but did find two suggestive ($P < 10^{-5}$) SNPs which correlated with response to HCTZ, and which were validated the African American group from the same studies [31]. rs177848 and rs177852 (in Caucasians and African Americans respectively) are located near *FOXA1*, which encodes a transcription factor, Forkhead Box A1, expressed in the collecting duct of the kidney, where it could play a role in water and solute handling [32]. Also identified in this analysis were rs11750990 and rs1049911 near *GJA1*, which encodes

 doi:10.20944/preprints201905.0035.v1

connexin 43, which functions in electrochemical coupling in myocardium and vascular smooth muscle. Lastly, a parallel survey of HTN candidate genes from this meta-analysis also implicated a series of SNPs near *HSD3B1*, whose gene product has a role in aldosterone synthesis [31].

Inhibitors of the renin-angiotensin system

The renin angiotensin system (RAS) plays a key role in BP regulation and the pathophysiology of HTN, and understandably this well-defined pathway has attracted early and ongoing attention in candidate gene studies as to whether genetic variation predicts response to a variety of antihypertensive classes, especially angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs). Initial interest was focused on a polymorphism of the angiotensin converting enzyme (ACE) gene, in which the insertion (I) variant in intron 16 (mean allele frequency (MAF) approximately 45%) has been associated with a significantly lower serum ACE level than the corresponding deletion (D) polymorphism [33]. Although initially several small and older studies suggested that those with the II genotype, identified by SNP rs1799752, had a stronger ACEI and ARB BP response [34-37], multiple larger and more recent studies have suggested there is actually no relationship [38-43]. Likewise, the literature has also failed to consistently show a role for variants of angiotensinogen (*AGT*) or variants of angiotensin II receptors *AGTR1* or *AGTR2* [44]. However, there have been two separate studies in Asian populations showing that variants in the renin (*REN*) gene affect BP response to valsartan. Here the CC genotype of the C-5312-T polymorphism was associated with greater DBP response, as well as a smaller compensatory increase in serum renin levels after treatment, which lends some biologic plausibility to these results [40,45,46].

 doi:10.20944/preprints201905.0035.v1

More recently, an intriguing finding from the GENRES study of in Finnish men randomized to several different antihypertensive drugs found in an unbiased genome analysis that carriers of a C allele at rs3814995 had greater BP response to losartan [47]. This class effect was replicated in American and European cohorts, and also in a separate analysis of Finnish patients in the LIFE (Losartan Intervention For Endpoint reduction in Hypertension) trial [48]. rs3814995 is a SNP within *NPHS1*, where the A allele codes for a missense mutation from glutamine to lysine at amino acid 117 in nephrin, a crucial protein in the glomerular slit diaphragm. This variant is considerably more common in Caucasian versus African American populations (MAF 0.30 versus 0.09) and mutations in this gene are responsible for one type of congenital nephrotic syndrome of the Finnish type [49]. The biological effect of this mutation on BP regulation has not been explored, but is interesting given the fact that ARBs have the clear effects on glomerular hemodynamics. Overall however, given the considerable knowledge about the physiology of the RAS, it is surprising that so few genes have been found to be relevant for predicting BP response to ACEIs and ARBs.

Beta blockers

Data supporting the influence of several genetic variants on the response to beta blockers is intriguing. The gene *ADRB1* codes for the β1 receptor, and two SNPs within this gene were originally identified in population studies as a risk factor for HTN [50]. The A allele at rs1801252 leads to a Ser49 variant, which leads to increased receptor internalization, while the C allele at rs18011253 results in the Arg389Gly variant, which causes less downstream signaling to adenylyl cyclase. Multiple studies have shown that the Arg389 and/or the Ser49Arg389 haplotype are

 doi:10.20944/preprints201905.0035.v1

associated with significantly better blood pressure response to beta blockers [51-54]. Importantly, analysis of the INVEST trial found that participants with the Ser49/Arg389 haplotype was associated with higher mortality when treated with a verapamil based strategy, as opposed to a beta blockers [55]. This validation in clinical outcomes, in concordance with a greater BP effect and firm biologic role, makes the case for this genetic variant highly persuasive. Nevertheless, some smaller studies, as well as analysis of the above SNPs in a 1729 patient cohort in the LIFE trial, have not supported a role for ADRB1 in BP control [41,56,57]. In contrast, studies of polymorphisms in or near the β2 receptor ADRB2, which has less expression in the heart, but more widespread distribution in the vasculature, have shown a less convincing and weaker relationship with response to beta blockers [41,58-60].

Another gene important in β1 receptor function is G protein-coupled receptor kinase 4 (*GRK4*), a kinase which restores β1 receptor activity after dephosphorylation by regulatory G kinases. Polymorphisms in *GRK4* (rs2960306 and rs1024323) were initially found in an analysis of the AASK study (African American Study of Kidney Disease and Hypertension) to influence the time to BP control with metoprolol, although this was seen only in men [61]. The AASK trial enrolled African Americans with hypertensive nephrosclerosis and thus by design focused on individuals with poor kidney function. This finding was clarified in a mixed race populations in the PEAR1 study, which had excluded individuals with abnormal kidney function [62]. Here the number of copies of the 65Leu142Val haplotype of rs2960306/rs1024323 correlated with decreased DBP responsiveness to atenolol (-9.1, -6.8, and -5.3 mm Hg in those with 0, 1, and 2 copies), an effect present in either gender. Furthermore the 486Val variant (rs1801058) was found in the INVEST trial to correlate with worse

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 May 2019 doi:10.20944/preprints201905.0035.v1

cardiovascular outcomes (OR 2.29, 95% CI 1.48 – 3.55), although this was seen in those getting either atenolol or verapamil.

Beyond the above genes which have a known biologic mechanism in adrenergic signaling, several other genes have emerged from unbiased analyses. One key study identified two SNPs which influenced response to beta blocker monotherapy in a combined African American cohort from the PEAR1 and PEAR2 studies. These SNPs were successfully validated in a second group of patients from PEAR1 in whom atenolol was added after HCTZ. rs201279313, a deletion of TTA in an intron of *SLC25A31*, was associated with a greater DBP response ($p=2.5 \times 10^{-8}$ in combined meta-analysis) [12]. This gene codes for a mitochondrial membrane ATP/ADP transporter. This study also found that the deletion variant of rs11313667 correlated with better SBP response to beta blockers ($p=7.2 \times 10^{-8}$). rs11313667 is intronic to the gene *LRRC15*, which encodes leucine rich repeat containing 15, a glycoprotein normally associated with placenta and cancers. Although the biologic basis of this effect is unknown, it could also be mediated via nearby genes, such as *GP5* (platelet glycoprotein V), which mediates the adhesion platelets to the endothelium and has been reported to be elevated in HTN [63].

Another example of the use of an unbiased GWAS to discover a gene influencing BP response is the gene *PTPRD*. Analysis of the Caucasian cohort of patients from the PEAR1 study found that SNP rs12346562, located upstream of *PTPRD*, correlates with improved BP response to beta blocker ($p=3.2 \times 10^{-6}$), with an opposite direction of effect seen in HCTZ [64]. This finding was confirmed in the Finnish population of the GENRES study; rs12346562 was also found to be linked with resistant

 doi:10.20944/preprints201905.0035.v1

HTN in the INVEST participants. *PTPRD* codes for receptor-type protein tyrosine phosphatase receptor delta, which has been found to have roles in neuron growth and guidance as well as malignant glioma, although through its involvement in the STAT3 pathway could possibly play a role in intrarenal RAS signaling [65]. Further support for this is given by the identification of a SNP rs10739150 downstream of *PTPRD* that correlates with BP responsiveness in the African American group from this study ($p=8.3 \times 10^{-6}$).

The Caucasian cohort from the PEAR1 study was analyzed to determine if a selected set of 37 SNPs previously associated with baseline HTN predicted BP response to atenolol or HCTZ. While none of these SNPs achieved genome wide significance, six did reach nominal significance. Of these, rs1458038, near the *FGF5* gene (Fibroblast Growth Factor 5), had the most powerful effect. The T allele of rs1458038 was significantly associated with better BP response to atenolol, while being associated with decreased response to HCTZ [66]. The relationship of this SNP to HTN at baseline in prior studies, the opposite directions of effect in different drug classes, and the strong linear relationship between the number of T alleles and both SBP and DBP response all support a likely association. This analysis additionally combined several others of these significant SNPs to calculate genetic scores accounting for 8.5% and 4.3% of the variation in SBP response to atenolol and HCTZ respectively. Of note, none of these variants had significant associations in the African American population within PEAR1. This level of prediction for BP response is considerably stronger than what has been observed for a risk score explaining the degree of untreated BP at baseline, which was estimated to be approximately 2.2% using the combined effect of 116 independent loci [67].

 doi:10.20944/preprints201905.0035.v1

Calcium channel blockers (CCBs)

Less work has directly examined the genetic predictors of CCB antihypertensive effect. However, longer term studies of cardiovascular outcomes such as the INVEST study has given us valuable information about the genetic influence on the ability of CCBs to reduce mortality. This study was an international multiracial comparison of verapamil versus atenolol in patients with HTN and CAD. The gene *KCNMB1* encodes the beta 1 subunit of the BK channel, and mutations within this gene were previously known to lead to HTN and left ventricular hypertrophy [68-70]. Thus variants of this gene were examined as to the effect on cardiovascular outcomes [71]. Carriers of rs11739136, which causes a glu65lys translocation in *KCNMB1*, achieved target BP control faster when treated with verapamil, but not atenolol. Carriers of rs2301149, which have a val110leu translocation in *KCNMB1*, had significantly lower rates of nonfatal MI when treated with verapamil, but not atenolol. Thus two nonsynonymous SNPs from this gene are associated with altered responsiveness to verapamil.

The gene *CACNA1C* encodes the alpha1C subunit of the L-type calcium channel, which is strongly expressed in heart and vascular smooth muscle and is the main target of calcium channel blockers. Eight variants of this gene were examined in the INVEST cohort. Of these, variation at rs1051375 correlated with outcomes, specifically a composite of death, nonfatal myocardial infarction, and nonfatal stroke [72]. The AA haplotype of this SNP had a reduction in composite primary outcomes to a hazard ratio of 0.54 (95% CI 0.32-0.92), while the GG haplotype had a hazard ratio of 4.59 (95% CI 1.67-12.67). The combination of previously known biologic relevance and the demonstration that these variants have relatively large effects on long term patient outcomes makes

 doi:10.20944/preprints201905.0035.v1

these findings highly relevant. The functionally related gene *CACNB2*, which encodes the regulatory beta-2 subunit of the voltage gated calcium channel, was also suggested to have a role in an analysis from INVEST. The GG haplotype of rs3129507, located within the promoter region of *CACNB2*, was associated with an increase in adverse cardiovascular outcomes in the verapamil group (HR 2.35, 95% CI 1.19-4.66, p = 0.014) [73]. A second SNP in this gene, rs11014166, was associated with outcome differences within the Hispanic subpopulation of this study. While BP response was not directly tracked as an outcome measure in these studies, the differences in outcome seen only in the verapamil treated group suggest a genetic basis for differential sensitivity to calcium channel blockers with these variants.

While the above findings were all directed at biologically based candidate genes, one study of a Caucasian cohort from the INVEST study used a GWAS of nonsynonymous SNPs to develop a risk score to identify differential mortality benefits with a CCB versus beta blocker treatment [74]. The derived risk score was based on the additive effect of three novel variants: rs16982743, rs893184, and rs4525, respectively located within *SIGLEC12*, *A1BG*, and *F5*. This score ranged from 0-3; a score of 0-1 was associated with improved outcomes in those treated with a CCB (OR 0.60, 95% CI 0.42–0.86), while a score of 2-3 was significantly associated with worse cardiovascular outcomes with a CCB versus a beta blocker (OR 1.31, 95% CI 01.08–1.59). This initial identification of these three SNPs was validated in an analysis of the NORDIL cohort. While these genes do not yet have any known biologic role in BP regulation, other SNPs in F5 have been associated with baseline HTN [75]. This approach of combining the effect of multiple SNPs in a cumulative risk score may be an attractive approach in

 doi:10.20944/preprints201905.0035.v1

the future to personalize treatment recommendations for individual patients despite the modest affect size of individual genes.

Pharmacokinetic influences

In addition to candidates based on mechanism of action, the response to several BP drugs is known to be influenced by genes influencing their metabolism. Losartan is a prodrug metabolized by cytochrome P450 enzymes CYP2C9, and to a lesser degree CYP3A4, to its active form [76]. Variants in CYP2C9 have been found which are associated with markedly slow conversion of losartan to its active metabolite, with significantly reduced effects on blood pressure and proteinuria [41,45,77]. Metoprolol is primarily metabolized by CYP2D6, which has multiple variant alleles, some of which are nonfunctional or hypofunctional [78,79]. Individuals carrying hypofunctional alleles have been found to have higher metoprolol blood levels, as well as differences in diastolic blood pressure (DBP), heart rate, and QT interval [80,81]. Additionally increased copy number of CYP2D6 can cause some individuals to be rapid metabolizers of metoprolol [82]. Based on this, the Dutch pharmacogenomics working Group (DPWG) has formally recommended CYP2D6 testing with metoprolol [83]. We have an incomplete knowledge of genetic influences on the pharmacokinetics of most antihypertensive drugs, but variations in drug levels may not always translate into meaningful differences in drug effect. An example is carvedilol, which is also metabolized by CYP2D6, with resultant differences in carvedilol drug levels, although differences in BP or other clinical effects have not been consistently observed [60,84]. Amlodipine and verapamil are known to be metabolized by CYP3A4 and CYP3A5 [85,86]. Several gene variants in the former were associated with better BP control with amlodipine in women in the AASK trial [85]. Lastly,

 doi:10.20944/preprints201905.0035.v1

hydralazine metabolism is affected by variants in its phase II metabolizing enzyme N-acetyltransferase-2. Individuals carrying NAT2*5, *6, and *7 alleles, present in up to 90% of North Africans and 50% of Caucasians, are more likely to have high drug levels and greater blood pressure response [87,88].

Adverse effects

In addition to immediate and longer term effectiveness of antihypertensives, some work has been directed at uncovering genetic predictors of known adverse effects from these drugs. Single studies have implicated potential variants that predict HCTZ-induced hypokalemia, hyperuricemia, or dyslipidemia with HCTZ or atenolol [89-91]. These studies have not yet been validated, but one study examining a panel of 33 candidate genetic variants previously associated with fasting glucose in the general population found that rs340874, located upstream of *PROX1*, was associated with atenolol induced hyperglycemia with a Caucasian cohort of the PEAR1 study [92]. *PROX1* encodes prospero homeobox 1, which has a role in embryologic development of liver and pancreas, and may be involved in liver gluconeogenesis [93]. Additionally, an association between thiazide induced hyperglycemia and variants in renal potassium channel *KCNJ1* was also suggested in an analysis of several candidate genes [94]. Subsequently, an analysis the African American cohort of the PEAR1 study found that variation at rs17137967, located within an intron of *KCNJ1*, was associated with thiazide induced new onset diabetes, subsequently confirmed in a multiracial group from the INVEST study [95]. Other work has explored predictors of the common problem of ACE-I induced cough, based not on a GWAS approach but by focus on genes with possible biologic rationale. An earlier finding that differences in the promotor region of bradykinin B2 receptor (*BDKRB2*) has not

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 May 2019 doi:10.20944/preprints201905.0035.v1

been repeated by other groups [96-98]. More recently however, two SNPs within introns of *BDKRB2* have been implicated in ACE-I induced cough, as well as findings that variance at rs495828 upstream of the *ABO* gene can predict this adverse event [99-101]. Identification of patients at risk of adverse effects from antihypertensive drugs has not been nearly as well studied as genetic influences on drug efficacy, but could have a major impact on patient care and health care expenses.

Where do we go from here?

The above studies show the large and growing amount of knowledge we have gained about how genetic variation affects individual response to individual antihypertensive drugs. Several limitations in the growing literature on HTN pharmacogenomics remain however. The nature of BP itself makes it a challenging outcome measure to study, since it is constantly changing, and affected by diet, activity, posture, psychological stress, and a variety of other factors. This has been most notably identified in large hypertension registries from Spain and other European countries where home, office, and 24 hour ambulatory BP measures configure different BP profiles [102,103]. Some studies, such as the PEAR trials, have make a thorough effort to address this by tracking BP taken by patients manually or by automated cuff at home. Of course, short term BP measurement is a surrogate endpoint, while the morbidity and mortality of patients is our ultimate concern. Trials such as INVEST and NORDIL have addressed this and given us key data on the influence of genetic variation on long term outcomes.

The generalizability of these findings is limited by the exclusion of sicker patients with more complex comorbidities in these trials. For instance, with the exception of the AASK trial, little

 doi:10.20944/preprints201905.0035.v1

pharmacogenomic data exist in the significant proportion of hypertensive patients with chronic kidney disease. As well, patients with resistant HTN (requiring more than three drugs for control) is another important group that may behave differently that what the above trials suggest, although some recent work is beginning to address this [104-106]. The identification of some novel genes also advances our understanding of human biology. Furthermore, another limitation to the GWAS approach is that using genetic arrays of known SNPs by definition excludes rare variants with allele frequencies < 0.05, thus inevitably the influence of rare but potentially powerful variants will not been detected. This may change as the cost of whole exon or whole genome sequencing becomes more feasible in the near future. Perhaps the greatest challenge is simply bringing together the vast amount of genetic information these many studies have now generated. Increasingly, work has combined cohorts from multiple studies to increase overall statistical power. While inevitably there are concerns about heterogeneity between different studies, this is clearly a step forward. The ICAPS (International Consortium for Antihypertensives Pharmacogenomics Studies) consortium, founded in 2012, has been a key force in advancing this work. ICAPS now has 29 clinical trials with 345,000 participants' data available for analysis. These better powered analyses allows calculation of risk scores using weighted combinations of multiple allelic variants which can better predict the response to different blood pressure agents [74,107]. Inclusion of other demographic or clinical data in such a score could further enhance accuracy of these models.

Despite the valuable information obtained through the work in this field, translating this into clinical practice to improve treatment of HTN remains a challenge. Reaching expert consensus in clinical guidelines requires weighing clinical benefits, potential adverse effects, and cost. While

 doi:10.20944/preprints201905.0035.v1

pharmacogenetics testing has obvious appeal in diseases like cancer, this is a situation where drug efficacy may have immediate impact on short term survival and drug toxicity is potentially quite high. CPIC (Clinical Pharmacogenetics Implementation Consortium) is an organization which reviews pharmacogenetic literature and makes recommendations regarding the use of this data in medical practice. As of now CPIC does not recommend any pharmacogenomic testing in the treatment of HTN. While the individual impact of genetic information to guide hypertensive treatment may not always make a vast difference to individual patients, the total impact is amplified by the vast number of patients with HTN.

One clear obstacle is the cost of genetic testing. While advancing technology has made genetic testing vastly less expensive than even five years ago, obtaining pharmacogenetics information on individual patients will still ultimately require insurance coverage for the vast majority of cases. Another impediment is that when genetic information becomes routinely available, individual physicians may vary widely in their comfort level interpreting and actually using pharmacogenomic data to make treatment decisions for their patients. Many current physicians had their medical training in an era before the sequencing of the human genome was achievable, and medical curricula did not emphasize medical genetics outside the handful of monogenic diseases. Explaining to patients the rationale and use of genetic testing presents unique challenges. Without an understanding, familiarity, and trust of new types of testing, providers may continue their current practice of prescribing antihypertensives based on trial and error. Thus it may be more realistic for clinical HTN specialists at academic medical centers to be the first group of physicians to implement

 doi:10.20944/preprints201905.0035.v1

pharmacogenomic information. Patients with difficult to control HTN are a subset in whom this approach may be the most natural, as well as being a group who may have the most to gain [104].

Despite these difficulties, a streamlined pharmacogenomic approach to get hypertensive patients on the most effective, efficient, and well tolerated drug regimen would have great benefits. This would result in fewer patient visits to readjust BP medications, fewer drugs per patient, and likely better compliance with their medical regimen. Better BP control would doubtless lead to fewer cardiovascular and renal complications and thus great improvement in quality of life and longevity [108-110]. Given the vast numbers of patients with HTN, this would as well result in enormous cost savings, with one recent economic analysis estimating national cost savings of $42 billion/year [111]. While this expectation appears straightforward, demonstration of such improved outcomes in clinical trials would be a powerful stimulus to bring pharmacogenomics into clinical use in patients with HTN.

Supplementary Materials: none

Author Contributions: writing—original draft preparation, P.C.; writing—review and editing, P.C. and A.C.;

Funding: This research received no external funding

 doi:10.20944/preprints201905.0035.v1

Acknowledgments: The authors wish to thank Michael Eadon M.D. for helpful discussions of this subject matter.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
RAS	renin-angiotensin system
HTN	Hypertension
GWAS	genome wide association study
ACE-Is	angiotensin converting enzyme inhibitors
ARBs	angiotensin receptor blockers
MAF	mean allele frequency
CCBs	calcium channel blockers
DBP	diastolic blood pressure (DBP)
DPWG	Dutch pharmacogenomics working Group
ICAPS	International Consortium for Antihypertensives Pharmacogenomics Studies
CPIC	Clinical Pharmacogenetics Implementation Consortium

References

1. Nguyen, T.; Lau, D.C. The obesity epidemic and its impact on hypertension. *Can J Cardiol* **2012**, *28*, 326-333, doi:10.1016/j.cjca.2012.01.001.

2. Chapman, A.B.; Schwartz, G.L.; Boerwinkle, E.; Turner, S.T. Predictors of antihypertensive response to a standard dose of hydrochlorothiazide for essential hypertension. *Kidney Int* **2002**, *61*, 1047-1055, doi:10.1046/j.1523-1755.2002.00200.x.
3. Snieder, H.; Hayward, C.S.; Perks, U.; Kelly, R.P.; Kelly, P.J.; Spector, T.D. Heritability of central systolic pressure augmentation: a twin study. *Hypertension* **2000**, *35*, 574-579.
4. Ohta, A.; Schumacher, F.R.; Mehellou, Y.; Johnson, C.; Knebel, A.; Macartney, T.J.; Wood, N.T.; Alessi, D.R.; Kurz, T. The CUL3-KLHL3 E3 ligase complex mutated in Gordon's hypertension syndrome interacts with and ubiquitylates WNK isoforms: disease-causing mutations in KLHL3 and WNK4 disrupt interaction. *Biochem J* **2013**, *451*, 111-122, doi:10.1042/BJ20121903.
5. Yamashita, Y.; Koga, M.; Takeda, Y.; Enomoto, N.; Uchida, S.; Hashimoto, K.; Yamano, S.; Dohi, K.; Marumo, F.; Sasaki, S. Two sporadic cases of Liddle's syndrome caused by De novo ENaC mutations. *Am J Kidney Dis* **2001**, *37*, 499-504.
6. Choi, M.; Scholl, U.I.; Yue, P.; Bjorklund, P.; Zhao, B.; Nelson-Williams, C.; Ji, W.; Cho, Y.; Patel, A.; Men, C.J., et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* **2011**, *331*, 768-772, doi:10.1126/science.1198785.
7. Mune, T.; Rogerson, F.M.; Nikkila, H.; Agarwal, A.K.; White, P.C. Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase. *Nat Genet* **1995**, *10*, 394-399, doi:10.1038/ng0895-394.
8. Rich, G.M.; Ulick, S.; Cook, S.; Wang, J.Z.; Lifton, R.P.; Dluhy, R.G. Glucocorticoid-remediable aldosteronism in a large kindred: clinical spectrum and diagnosis using a characteristic biochemical phenotype. *Ann Intern Med* **1992**, *116*, 813-820.
9. White, H.L.; de Boer, R.A.; Maqbool, A.; Greenwood, D.; van Veldhuisen, D.J.; Cuthbert, R.; Ball, S.G.; Hall, A.S.; Balmforth, A.J. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. *Eur J Heart Fail* **2003**, *5*, 463-468.
10. Evangelou, E.; Warren, H.R.; Mosen-Ansorena, D.; Mifsud, B.; Pazoki, R.; Gao, H.; Ntritsos, G.; Dimou, N.; Cabrera, C.P.; Karaman, I., et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* **2018**, *50*, 1412-1425, doi:10.1038/s41588-018-0205-x.
11. Duarte, J.D.; Turner, S.T.; Tran, B.; Chapman, A.B.; Bailey, K.R.; Gong, Y.; Gums, J.G.; Langaee, T.Y.; Beitelshees, A.L.; Cooper-Dehoff, R.M., et al. Association of chromosome 12 locus with antihypertensive response to hydrochlorothiazide may involve differential YEATS4 expression. *Pharmacogenomics J* **2013**, *13*, 257-263, doi:10.1038/tpj.2012.4.
12. Gong, Y.; Wang, Z.; Beitelshees, A.L.; McDonough, C.W.; Langaee, T.Y.; Hall, K.; Schmidt, S.O.; Curry, R.W., Jr.; Gums, J.G.; Bailey, K.R., et al. Pharmacogenomic Genome-Wide Meta-Analysis of Blood Pressure Response to beta-Blockers in Hypertensive African Americans. *Hypertension* **2016**, *67*, 556-563, doi:10.1161/hypertensionaha.115.06345.
13. Turner, S.T.; Boerwinkle, E.; O'Connell, J.R.; Bailey, K.R.; Gong, Y.; Chapman, A.B.; McDonough, C.W.; Beitelshees, A.L.; Schwartz, G.L.; Gums, J.G., et al. Genomic association analysis of common variants influencing antihypertensive response to hydrochlorothiazide. *Hypertension* **2013**, *62*, 391-397, doi:10.1161/HYPERTENSIONAHA.111.00436.

14. Sa, A.C.C.; Webb, A.; Gong, Y.; McDonough, C.W.; Datta, S.; Langaee, T.Y.; Turner, S.T.; Beitelshees, A.L.; Chapman, A.B.; Boerwinkle, E., et al. Whole Transcriptome Sequencing Analyses Reveal Molecular Markers of Blood Pressure Response to Thiazide Diuretics. *Sci Rep* **2017**, *7*, 16068, doi:10.1038/s41598-017-16343-z.
15. Sa, A.C.C.; Webb, A.; Gong, Y.; McDonough, C.W.; Shahin, M.H.; Datta, S.; Langaee, T.Y.; Turner, S.T.; Beitelshees, A.L.; Chapman, A.B., et al. Blood pressure signature genes and blood pressure response to thiazide diuretics: results from the PEAR and PEAR-2 studies. *BMC Med Genomics* **2018**, *11*, 55, doi:10.1186/s12920-018-0370-x.
16. Fava, C.; von Wowern, F.; Berglund, G.; Carlson, J.; Hedblad, B.; Rosberg, L.; Burri, P.; Almgren, P.; Melander, O. 24-h ambulatory blood pressure is linked to chromosome 18q21-22 and genetic variation of NEDD4L associates with cross-sectional and longitudinal blood pressure in Swedes. *Kidney Int* **2006**, *70*, 562-569, doi:10.1038/sj.ki.5001590.
17. Luo, F.; Wang, Y.; Wang, X.; Sun, K.; Zhou, X.; Hui, R. A functional variant of NEDD4L is associated with hypertension, antihypertensive response, and orthostatic hypotension. *Hypertension* **2009**, *54*, 796-801, doi:10.1161/hypertensionaha.109.135103.
18. Russo, C.J.; Melista, E.; Cui, J.; DeStefano, A.L.; Bakris, G.L.; Manolis, A.J.; Gavras, H.; Baldwin, C.T. Association of NEDD4L ubiquitin ligase with essential hypertension. *Hypertension* **2005**, *46*, 488-491, doi:10.1161/01.HYP.0000178594.63193.c0.
19. Dahlberg, J.; Sjogren, M.; Hedblad, B.; Engstrom, G.; Melander, O. Genetic variation in NEDD4L, an epithelial sodium channel regulator, is associated with cardiovascular disease and cardiovascular death. *J Hypertens* **2014**, *32*, 294-299, doi:10.1097/hjh.0000000000000044.
20. Svensson-Farbom, P.; Wahlstrand, B.; Almgren, P.; Dahlberg, J.; Fava, C.; Kjeldsen, S.; Hedner, T.; Melander, O. A functional variant of the NEDD4L gene is associated with beneficial treatment response with beta-blockers and diuretics in hypertensive patients. *J Hypertens* **2011**, *29*, 388-395, doi:10.1097/HJH.0b013e3283410390.
21. McDonough, C.W.; Burbage, S.E.; Duarte, J.D.; Gong, Y.; Langaee, T.Y.; Turner, S.T.; Gums, J.G.; Chapman, A.B.; Bailey, K.R.; Beitelshees, A.L., et al. Association of variants in NEDD4L with blood pressure response and adverse cardiovascular outcomes in hypertensive patients treated with thiazide diuretics. *J Hypertens* **2013**, *31*, 698-704, doi:10.1097/HJH.0b013e32835e2a71.
22. Turner, S.T.; Bailey, K.R.; Fridley, B.L.; Chapman, A.B.; Schwartz, G.L.; Chai, H.S.; Sicotte, H.; Kocher, J.P.; Rodin, A.S.; Boerwinkle, E. Genomic association analysis suggests chromosome 12 locus influencing antihypertensive response to thiazide diuretic. *Hypertension* **2008**, *52*, 359-365, doi:10.1161/HYPERTENSIONAHA.107.104273.
23. Wang, Y.; Jin, J.; Chung, M.W.H.; Feng, L.; Sun, H.; Hao, Q. Identification of the YEATS domain of GAS41 as a pH-dependent reader of histone succinylation. *Proc Natl Acad Sci U S A* **2018**, *115*, 2365-2370, doi:10.1073/pnas.1717664115.
24. Wynne, B.M.; McCarthy, C.G.; Szasz, T.; Molina, P.A.; Chapman, A.B.; Webb, R.C.; Klein, J.D.; Hoover, R.S. Protein kinase Calpha deletion causes hypotension and decreased vascular contractility. *J Hypertens* **2018**, *36*, 510-519, doi:10.1097/HJH.0000000000001596.

25. Klemke, M.; Kehlenbach, R.H.; Huttner, W.B. Two overlapping reading frames in a single exon encode interacting proteins--a novel way of gene usage. *Embo J* **2001**, *20*, 3849-3860, doi:10.1093/emboj/20.14.3849.
26. Nunn, N.; Feetham, C.H.; Martin, J.; Barrett-Jolley, R.; Plagge, A. Elevated blood pressure, heart rate and body temperature in mice lacking the XLalphas protein of the Gnas locus is due to increased sympathetic tone. *Exp Physiol* **2013**, *98*, 1432-1445, doi:10.1113/expphysiol.2013.073064.
27. Chittani, M.; Zaninello, R.; Lanzani, C.; Frau, F.; Ortu, M.F.; Salvi, E.; Fresu, G.; Citterio, L.; Braga, D.; Piras, D.A., et al. TET2 and CSMD1 genes affect SBP response to hydrochlorothiazide in never-treated essential hypertensives. *J Hypertens* **2015**, *33*, 1301-1309, doi:10.1097/HJH.0000000000000541.
28. Turner, S.T.; Schwartz, G.L.; Chapman, A.B.; Boerwinkle, E. C825T polymorphism of the G protein beta(3)-subunit and antihypertensive response to a thiazide diuretic. *Hypertension* **2001**, *37*, 739-743.
29. Shahin, M.H.; Sa, A.C.; Webb, A.; Gong, Y.; Langaee, T.; McDonough, C.W.; Riva, A.; Beitleshees, A.L.; Chapman, A.B.; Gums, J.G., et al. Genome-Wide Prioritization and Transcriptomics Reveal Novel Signatures Associated With Thiazide Diuretics Blood Pressure Response. *Circ Cardiovasc Genet* **2017**, *10*, doi:10.1161/CIRCGENETICS.116.001404.
30. Matayoshi, T.; Kamide, K.; Takiuchi, S.; Yoshii, M.; Miwa, Y.; Takami, Y.; Tanaka, C.; Banno, M.; Horio, T.; Nakamura, S., et al. The thiazide-sensitive Na(+)-Cl(-) cotransporter gene, C1784T, and adrenergic receptor-beta3 gene, T727C, may be gene polymorphisms susceptible to the antihypertensive effect of thiazide diuretics. *Hypertens Res* **2004**, *27*, 821-833.
31. Salvi, E.; Wang, Z.; Rizzi, F.; Gong, Y.; McDonough, C.W.; Padmanabhan, S.; Hiltunen, T.P.; Lanzani, C.; Zaninello, R.; Chittani, M., et al. Genome-Wide and Gene-Based Meta-Analyses Identify Novel Loci Influencing Blood Pressure Response to Hydrochlorothiazide. *Hypertension* **2017**, *69*, 51-59, doi:10.1161/hypertensionaha.116.08267.
32. Gonzalez-Nunez, D.; Morales-Ruiz, M.; Leivas, A.; Hebert, S.C.; Poch, E. In vitro characterization of aldosterone and cAMP effects in mouse distal convoluted tubule cells. *Am J Physiol Renal Physiol* **2004**, *286*, F936-944, doi:10.1152/ajprenal.00070.2003.
33. Rigat, B.; Hubert, C.; Alhenc-Gelas, F.; Cambien, F.; Corvol, P.; Soubrier, F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* **1990**, *86*, 1343-1346, doi:10.1172/jci114844.
34. Jacobsen, P.; Rossing, K.; Rossing, P.; Tarnow, L.; Mallet, C.; Poirier, O.; Cambien, F.; Parving, H.H. Angiotensin converting enzyme gene polymorphism and ACE inhibition in diabetic nephropathy. *Kidney Int* **1998**, *53*, 1002-1006, doi:10.1111/j.1523-1755.1998.00847.x.
35. Mizuiri, S.; Hemmi, H.; Inoue, A.; Takano, M.; Kadomatsu, S.; Tanimoto, H.; Tanegashima, M.; Hayashi, I.; Fushimi, T.; Hasegawa, A. Renal hemodynamic changes induced by captopril and angiotensin-converting enzyme gene polymorphism. *Nephron* **1997**, *75*, 310-314, doi:10.1159/000189554.

36. O'Toole, L.; Stewart, M.; Padfield, P.; Channer, K. Effect of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene on response to angiotensin-converting enzyme inhibitors in patients with heart failure. *Journal of cardiovascular pharmacology* **1998**, *32*, 988-994.
37. Volkan-Salanci, B.; Dagdelen, S.; Alikasifoglu, M.; Erbas, T.; Hayran, M.; Erbas, B. Impact of renin-angiotensin system polymorphisms on renal haemodynamic responsiveness to acute angiotensin-converting enzyme inhibition in type 2 diabetes mellitus. *J Renin Angiotensin Aldosterone Syst* **2009**, *10*, 41-50, doi:10.1177/1470320309102326.
38. Arnett, D.K.; Davis, B.R.; Ford, C.E.; Boerwinkle, E.; Leiendecker-Foster, C.; Miller, M.B.; Black, H.; Eckfeldt, J.H. Pharmacogenetic association of the angiotensin-converting enzyme insertion/deletion polymorphism on blood pressure and cardiovascular risk in relation to antihypertensive treatment: the Genetics of Hypertension-Associated Treatment (GenHAT) study. *Circulation* **2005**, *111*, 3374-3383, doi:10.1161/CIRCULATIONAHA.104.504639.
39. Filigheddu, F.; Argiolas, G.; Bulla, E.; Troffa, C.; Bulla, P.; Fadda, S.; Zaninello, R.; Degortes, S.; Frau, F.; Pitzoi, S., et al. Clinical variables, not RAAS polymorphisms, predict blood pressure response to ACE inhibitors in Sardinians. *Pharmacogenomics* **2008**, *9*, 1419-1427, doi:10.2217/14622416.9.10.1419.
40. Konoshita, T.; Kato, N.; Fuchs, S.; Mizuno, S.; Aoyama, C.; Motomura, M.; Makino, Y.; Wakahara, S.; Inoki, I.; Miyamori, I., et al. Genetic variant of the Renin-Angiotensin system and diabetes influences blood pressure response to Angiotensin receptor blockers. *Diabetes Care* **2009**, *32*, 1485-1490, doi:10.2337/dc09-0348.
41. Nordestgaard, B.G.; Kontula, K.; Benn, M.; Dahlof, B.; de Faire, U.; Edelman, J.M.; Eliasson, E.; Fyhrquist, F.; Hille, D.A.; Ibsen, H., et al. Effect of ACE insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the LIFE study. *Pharmacogenet Genomics* **2010**, *20*, 77-85, doi:10.1097/FPC.0b013e328333f70b.
42. Redon, J.; Luque-Otero, M.; Martell, N.; Chaves, F.J. Renin-angiotensin system gene polymorphisms: relationship with blood pressure and microalbuminuria in telmisartan-treated hypertensive patients. *Pharmacogenomics J* **2005**, *5*, 14-20, doi:10.1038/sj.tpj.6500280.
43. Yu, H.; Zhang, Y.; Liu, G. Relationship between polymorphism of the angiotensin-converting enzyme gene and the response to angiotensin-converting enzyme inhibition in hypertensive patients. *Hypertens Res* **2003**, *26*, 881-886.
44. Hannila-Handelberg, T.; Kontula, K.K.; Paukku, K.; Lehtonen, J.Y.; Virtamo, J.; Tikkanen, I.; Hiltunen, T.P. Common genetic variations of the renin-angiotensin-aldosterone system and response to acute angiotensin I-converting enzyme inhibition in essential hypertension. *J Hypertens* **2010**, *28*, 771-779, doi:10.1097/HJH.0b013e328335c368.
45. Makino, Y.; Konoshita, T.; Omori, A.; Maegawa, N.; Nakaya, T.; Ichikawa, M.; Yamamoto, K.; Wakahara, S.; Ishizuka, T.; Onoe, T., et al. A Genetic Variant in the Distal Enhancer Region of the Human Renin Gene Affects Renin Expression. *PLoS One* **2015**, *10*, e0137469, doi:10.1371/journal.pone.0137469.
46. Rohman, M.S.; Dewi Satiti, I.A.; Widodo, N.; Lukitasari, M.; Sujuti, H. Genetic Variants of C-5312T REN Increased Renin Levels and Diastolic Blood Pressure Response to Angiotensin Receptor Blockers. *Int J Hypertens* **2015**, *2015*, 930631, doi:10.1155/2015/930631.

47. Hiltunen, T.P.; Donner, K.M.; Sarin, A.P.; Saarela, J.; Ripatti, S.; Chapman, A.B.; Gums, J.G.; Gong, Y.; Cooper-DeHoff, R.M.; Frau, F., et al. Pharmacogenomics of hypertension: a genome-wide, placebo-controlled cross-over study, using four classes of antihypertensive drugs. *Journal of the American Heart Association* **2015**, *4*, e001521, doi:10.1161/JAHA.115.001778.

48. Rimpela, J.M.; Kontula, K.K.; Fyhrquist, F.; Donner, K.M.; Tuiskula, A.M.; Sarin, A.P.; Mohney, R.P.; Stirdivant, S.M.; Hiltunen, T.P. Replicated evidence for aminoacylase 3 and nephrin gene variations to predict antihypertensive drug responses. *Pharmacogenomics* **2017**, *18*, 445-458, doi:10.2217/pgs-2016-0204.

49. Jalanko, H. Congenital nephrotic syndrome. *Pediatr Nephrol* **2009**, *24*, 2121-2128, doi:10.1007/s00467-007-0633-9.

50. Johnson, A.D.; Newton-Cheh, C.; Chasman, D.I.; Ehret, G.B.; Johnson, T.; Rose, L.; Rice, K.; Verwoert, G.C.; Launer, L.J.; Gudnason, V., et al. Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. *Hypertension* **2011**, *57*, 903-910, doi:10.1161/hypertensionaha.110.158667.

51. Johnson, J.A.; Zineh, I.; Puckett, B.J.; McGorray, S.P.; Yarandi, H.N.; Pauly, D.F. Beta 1-adrenergic receptor polymorphisms and antihypertensive response to metoprolol. *Clin Pharmacol Ther* **2003**, *74*, 44-52, doi:10.1016/s0009-9236(03)00068-7.

52. Liu, J.; Liu, Z.Q.; Yu, B.N.; Xu, F.H.; Mo, W.; Zhou, G.; Liu, Y.Z.; Li, Q.; Zhou, H.H. beta1-Adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension. *Clin Pharmacol Ther* **2006**, *80*, 23-32, doi:10.1016/j.clpt.2006.03.004.

53. Si, D.; Wang, J.; Xu, Y.; Chen, X.; Zhang, M.; Zhou, H. Association of common polymorphisms in beta1-adrenergic receptor with antihypertensive response to carvedilol. *J Cardiovasc Pharmacol* **2014**, *64*, 306-309, doi:10.1097/fjc.0000000000000119.

54. Wu, D.; Li, G.; Deng, M.; Song, W.; Huang, X.; Guo, X.; Wu, Z.; Wu, S.; Xu, J. Associations between ADRB1 and CYP2D6 gene polymorphisms and the response to beta-blocker therapy in hypertension. *J Int Med Res* **2015**, *43*, 424-434, doi:10.1177/0300060514563151.

55. Pacanowski, M.A.; Gong, Y.; Cooper-Dehoff, R.M.; Schork, N.J.; Shriver, M.D.; Langaee, T.Y.; Pepine, C.J.; Johnson, J.A. beta-adrenergic receptor gene polymorphisms and beta-blocker treatment outcomes in hypertension. *Clin Pharmacol Ther* **2008**, *84*, 715-721, doi:10.1038/clpt.2008.139.

56. Karlsson, J.; Lind, L.; Hallberg, P.; Michaelsson, K.; Kurland, L.; Kahan, T.; Malmqvist, K.; Ohman, K.P.; Nystrom, F.; Melhus, H. Beta1-adrenergic receptor gene polymorphisms and response to beta1-adrenergic receptor blockade in patients with essential hypertension. *Clin Cardiol* **2004**, *27*, 347-350.

57. O'Shaughnessy, K.M.; Fu, B.; Dickerson, C.; Thurston, D.; Brown, M.J. The gain-of-function G389R variant of the beta1-adrenoceptor does not influence blood pressure or heart rate response to beta-blockade in hypertensive subjects. *Clin Sci (Lond)* **2000**, *99*, 233-238.

58. de Groote, P.; Helbecque, N.; Lamblin, N.; Hermant, X.; Mc Fadden, E.; Foucher-Hossein, C.; Amouyel, P.; Dallongeville, J.; Bauters, C. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. *Pharmacogenet Genomics* **2005**, *15*, 137-142.

59. Iaccarino, G.; Izzo, R.; Trimarco, V.; Cipolletta, E.; Lanni, F.; Sorriento, D.; Iovino, G.L.; Rozza, F.; De Luca, N.; Priante, O., et al. Beta2-adrenergic receptor polymorphisms and treatment-induced regression of left ventricular hypertrophy in hypertension. *Clin Pharmacol Ther* **2006**, *80*, 633-645, doi:10.1016/j.clpt.2006.09.006.
60. Sehrt, D.; Meineke, I.; Tzvetkov, M.; Gultepe, S.; Brockmoller, J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. *Pharmacogenomics* **2011**, *12*, 783-795, doi:10.2217/pgs.11.20.
61. Bhatnagar, V.; O'Connor, D.T.; Brophy, V.H.; Schork, N.J.; Richard, E.; Salem, R.M.; Nievergelt, C.M.; Bakris, G.L.; Middleton, J.P.; Norris, K.C., et al. G-protein-coupled receptor kinase 4 polymorphisms and blood pressure response to metoprolol among African Americans: sex-specificity and interactions. *Am J Hypertens* **2009**, *22*, 332-338, doi:10.1038/ajh.2008.341.
62. Vandell, A.G.; Lobmeyer, M.T.; Gawronski, B.E.; Langaee, T.Y.; Gong, Y.; Gums, J.G.; Beitelshees, A.L.; Turner, S.T.; Chapman, A.B.; Cooper-DeHoff, R.M., et al. G protein receptor kinase 4 polymorphisms: beta-blocker pharmacogenetics and treatment-related outcomes in hypertension. *Hypertension* **2012**, *60*, 957-964, doi:10.1161/HYPERTENSIONAHA.112.198721.
63. Remkova, A.; Remko, M. The role of renin-angiotensin system in prothrombotic state in essential hypertension. *Physiol Res* **2010**, *59*, 13-23.
64. Gong, Y.; McDonough, C.W.; Beitelshees, A.L.; El Rouby, N.; Hiltunen, T.P.; O'Connell, J.R.; Padmanabhan, S.; Langaee, T.Y.; Hall, K.; Schmidt, S.O., et al. PTPRD gene associated with blood pressure response to atenolol and resistant hypertension. *J Hypertens* **2015**, *33*, 2278-2285, doi:10.1097/HJH.0000000000000714.
65. Satou, R.; Gonzalez-Villalobos, R.A. JAK-STAT and the renin-angiotensin system: The role of the JAK-STAT pathway in blood pressure and intrarenal renin-angiotensin system regulation. *Jakstat* **2012**, *1*, 250-256, doi:10.4161/jkst.22729.
66. Gong, Y.; McDonough, C.W.; Wang, Z.; Hou, W.; Cooper-DeHoff, R.M.; Langaee, T.Y.; Beitelshees, A.L.; Chapman, A.B.; Gums, J.G.; Bailey, K.R., et al. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study. *Circ Cardiovasc Genet* **2012**, *5*, 686-691, doi:10.1161/CIRCGENETICS.112.964080.
67. Ehret, G.B.; Munroe, P.B.; Rice, K.M.; Bochud, M.; Johnson, A.D.; Chasman, D.I.; Smith, A.V.; Tobin, M.D.; Verwoert, G.C.; Hwang, S.J., et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **2011**, *478*, 103-109, doi:10.1038/nature10405.
68. Gong, Y.; Beitelshees, A.L.; Wessel, J.; Langaee, T.Y.; Schork, N.J.; Johnson, J.A. Single nucleotide polymorphism discovery and haplotype analysis of Ca2+-dependent K+ channel beta-1 subunit. *Pharmacogenet Genomics* **2007**, *17*, 267-275, doi:10.1097/FPC.0b013e3280105235.
69. Nielsen, T.; Burgdorf, K.S.; Grarup, N.; Borch-Johnsen, K.; Hansen, T.; Jorgensen, T.; Pedersen, O.; Andersen, G. The KCNMB1 Glu65Lys polymorphism associates with reduced systolic and diastolic blood pressure in the Inter99 study of 5729 Danes. *J Hypertens* **2008**, *26*, 2142-2146, doi:10.1097/HJH.0b013e32830b894a.

70. Zhao, Q.; Wang, L.; Yang, W.; Chen, S.; Huang, J.; Fan, Z.; Li, H.; Lu, X.; Gu, D. Interactions among genetic variants from contractile pathway of vascular smooth muscle cell in essential hypertension susceptibility of Chinese Han population. *Pharmacogenet Genomics* **2008**, *18*, 459-466, doi:10.1097/FPC.0b013e3282f97fb2.

71. Beitelshees, A.L.; Gong, Y.; Wang, D.; Schork, N.J.; Cooper-Dehoff, R.M.; Langaee, T.Y.; Shriver, M.D.; Sadee, W.; Knot, H.J.; Pepine, C.J., et al. KCNMB1 genotype influences response to verapamil SR and adverse outcomes in the INternational VErapamil SR/Trandolapril STudy (INVEST). *Pharmacogenet Genomics* **2007**, *17*, 719-729, doi:10.1097/FPC.0b013e32810f2e3c.

72. Beitelshees, A.L.; Navare, H.; Wang, D.; Gong, Y.; Wessel, J.; Moss, J.I.; Langaee, T.Y.; Cooper-DeHoff, R.M.; Sadee, W.; Pepine, C.J., et al. CACNA1C gene polymorphisms, cardiovascular disease outcomes, and treatment response. *Circ Cardiovasc Genet* **2009**, *2*, 362-370, doi:10.1161/CIRCGENETICS.109.857839.

73. Niu, Y.; Gong, Y.; Langaee, T.Y.; Davis, H.M.; Elewa, H.; Beitelshees, A.L.; Moss, J.I.; Cooper-Dehoff, R.M.; Pepine, C.J.; Johnson, J.A. Genetic variation in the beta2 subunit of the voltage-gated calcium channel and pharmacogenetic association with adverse cardiovascular outcomes in the INternational VErapamil SR-Trandolapril STudy GENEtic Substudy (INVEST-GENES). *Circ Cardiovasc Genet* **2010**, *3*, 548-555, doi:10.1161/circgenetics.110.957654.

74. McDonough, C.W.; Gong, Y.; Padmanabhan, S.; Burkley, B.; Langaee, T.Y.; Melander, O.; Pepine, C.J.; Dominiczak, A.F.; Cooper-Dehoff, R.M.; Johnson, J.A. Pharmacogenomic association of nonsynonymous SNPs in SIGLEC12, A1BG, and the selectin region and cardiovascular outcomes. *Hypertension* **2013**, *62*, 48-54, doi:10.1161/HYPERTENSIONAHA.111.00823.

75. Ehret, G.B.; O'Connor, A.A.; Weder, A.; Cooper, R.S.; Chakravarti, A. Follow-up of a major linkage peak on chromosome 1 reveals suggestive QTLs associated with essential hypertension: GenNet study. *Eur J Hum Genet* **2009**, *17*, 1650-1657, doi:10.1038/ejhg.2009.94.

76. Yasar, U.; Tybring, G.; Hidestrand, M.; Oscarson, M.; Ingelman-Sundberg, M.; Dahl, M.L.; Eliasson, E. Role of CYP2C9 polymorphism in losartan oxidation. *Drug Metab Dispos* **2001**, *29*, 1051-1056.

77. Yasar, U.; Forslund-Bergengren, C.; Tybring, G.; Dorado, P.; Llerena, A.; Sjoqvist, F.; Eliasson, E.; Dahl, M.L. Pharmacokinetics of losartan and its metabolite E-3174 in relation to the CYP2C9 genotype. *Clin Pharmacol Ther* **2002**, *71*, 89-98, doi:10.1067/mcp.2002.121216.

78. Bradford, L.D. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* **2002**, *3*, 229-243, doi:10.1517/14622416.3.2.229.

79. Zhou, S.F. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet* **2009**, *48*, 689-723, doi:10.2165/11318030-000000000-00000.

80. Hamadeh, I.S.; Langaee, T.Y.; Dwivedi, R.; Garcia, S.; Burkley, B.M.; Skaar, T.C.; Chapman, A.B.; Gums, J.G.; Turner, S.T.; Gong, Y., et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. *Clin Pharmacol Ther* **2014**, *96*, 175-181, doi:10.1038/clpt.2014.62.

81. Rau, T.; Wuttke, H.; Michels, L.M.; Werner, U.; Bergmann, K.; Kreft, M.; Fromm, M.F.; Eschenhagen, T. Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a

prospective longitudinal study. *Clin Pharmacol Ther* **2009**, *85*, 269-272, doi:10.1038/clpt.2008.218.

82. Johansson, I.; Lundqvist, E.; Bertilsson, L.; Dahl, M.L.; Sjoqvist, F.; Ingelman-Sundberg, M. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci U S A* **1993**, *90*, 11825-11829.
83. Swen, J.J.; Nijenhuis, M.; de Boer, A.; Grandia, L.; Maitland-van der Zee, A.H.; Mulder, H.; Rongen, G.A.; van Schaik, R.H.; Schalekamp, T.; Touw, D.J., et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther* **2011**, *89*, 662-673, doi:10.1038/clpt.2011.34.
84. Baudhuin, L.M.; Miller, W.L.; Train, L.; Bryant, S.; Hartman, K.A.; Phelps, M.; Larock, M.; Jaffe, A.S. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. *Am J Cardiol* **2010**, *106*, 402-408, doi:10.1016/j.amjcard.2010.03.041.
85. Bhatnagar, V.; Garcia, E.P.; O'Connor, D.T.; Brophy, V.H.; Alcaraz, J.; Richard, E.; Bakris, G.L.; Middleton, J.P.; Norris, K.C.; Wright, J., et al. CYP3A4 and CYP3A5 polymorphisms and blood pressure response to amlodipine among African-American men and women with early hypertensive renal disease. *Am J Nephrol* **2010**, *31*, 95-103, doi:10.1159/000258688.
86. Langaee, T.Y.; Gong, Y.; Yarandi, H.N.; Katz, D.A.; Cooper-DeHoff, R.M.; Pepine, C.J.; Johnson, J.A. Association of CYP3A5 polymorphisms with hypertension and antihypertensive response to verapamil. *Clin Pharmacol Ther* **2007**, *81*, 386-391, doi:10.1038/sj.clpt.6100090.
87. Autrup, H. Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. *Mutat Res* **2000**, *464*, 65-76.
88. Spinasse, L.B.; Santos, A.R.; Suffys, P.N.; Muxfeldt, E.S.; Salles, G.F. Different phenotypes of the NAT2 gene influences hydralazine antihypertensive response in patients with resistant hypertension. *Pharmacogenomics* **2014**, *15*, 169-178, doi:10.2217/pgs.13.202.
89. Del-Aguila, J.L.; Beitelshees, A.L.; Cooper-Dehoff, R.M.; Chapman, A.B.; Gums, J.G.; Bailey, K.; Gong, Y.; Turner, S.T.; Johnson, J.A.; Boerwinkle, E. Genome-wide association analyses suggest NELL1 influences adverse metabolic response to HCTZ in African Americans. *Pharmacogenomics J* **2014**, *14*, 35-40, doi:10.1038/tpj.2013.3.
90. Del-Aguila, J.L.; Cooper-DeHoff, R.M.; Chapman, A.B.; Gums, J.G.; Beitelshees, A.L.; Bailey, K.; Turner, S.T.; Johnson, J.A.; Boerwinkle, E. Transethnic meta-analysis suggests genetic variation in the HEME pathway influences potassium response in patients treated with hydrochlorothiazide. *Pharmacogenomics J* **2015**, *15*, 153-157, doi:10.1038/tpj.2014.46.
91. Vandell, A.G.; McDonough, C.W.; Gong, Y.; Langaee, T.Y.; Lucas, A.M.; Chapman, A.B.; Gums, J.G.; Beitelshees, A.L.; Bailey, K.R.; Johnson, R.J., et al. Hydrochlorothiazide-induced hyperuricaemia in the pharmacogenomic evaluation of antihypertensive responses study. *J Intern Med* **2014**, *276*, 486-497, doi:10.1111/joim.12215.
92. Gong, Y.; McDonough, C.W.; Beitelshees, A.L.; Karnes, J.H.; O'Connell, J.R.; Turner, S.T.; Chapman, A.B.; Gums, J.G.; Bailey, K.R.; Boerwinkle, E., et al. PROX1 gene variant is associated with fasting glucose change after antihypertensive treatment. *Pharmacotherapy* **2014**, *34*, 123-130, doi:10.1002/phar.1355.

93. Song, K.H.; Li, T.; Chiang, J.Y. A Prospero-related homeodomain protein is a novel co-regulator of hepatocyte nuclear factor 4alpha that regulates the cholesterol 7alpha-hydroxylase gene. *J Biol Chem* **2006**, *281*, 10081-10088, doi:10.1074/jbc.M513420200.
94. Maitland-van der Zee, A.H.; Turner, S.T.; Schwartz, G.L.; Chapman, A.B.; Klungel, O.H.; Boerwinkle, E. Demographic, environmental, and genetic predictors of metabolic side effects of hydrochlorothiazide treatment in hypertensive subjects. *Am J Hypertens* **2005**, *18*, 1077-1083, doi:10.1016/j.amjhyper.2005.02.012.
95. Karnes, J.H.; McDonough, C.W.; Gong, Y.; Vo, T.T.; Langaee, T.Y.; Chapman, A.B.; Gums, J.G.; Beitelshees, A.L.; Bailey, K.R.; Del-Aguila, J.L., et al. Association of KCNJ1 variation with change in fasting glucose and new onset diabetes during HCTZ treatment. *Pharmacogenomics J* **2013**, *13*, 430-436, doi:10.1038/tpj.2012.34.
96. Lee, Y.J.; Tsai, J.C. Angiotensin-converting enzyme gene insertion/deletion, not bradykinin B2 receptor -58T/C gene polymorphism, associated with angiotensin-converting enzyme inhibitor-related cough in Chinese female patients with non-insulin-dependent diabetes mellitus. *Metabolism* **2001**, *50*, 1346-1350.
97. Mukae, S.; Itoh, S.; Aoki, S.; Iwata, T.; Nishio, K.; Sato, R.; Katagiri, T. Association of polymorphisms of the renin-angiotensin system and bradykinin B2 receptor with ACE-inhibitor-related cough. *J Hum Hypertens* **2002**, *16*, 857-863, doi:10.1038/sj.jhh.1001486.
98. Woo, S.W.; Bang, S.; Chung, M.W.; Jin, S.K.; Kim, Y.S.; Lee, S.H. Lack of association between ACE and bradykinin B2 receptor gene polymorphisms and ACE inhibitor-induced coughing in hypertensive Koreans. *J Clin Pharm Ther* **2009**, *34*, 561-567, doi:10.1111/j.1365-2710.2009.01028.x.
99. Grilo, A.; Saez-Rosas, M.P.; Santos-Morano, J.; Sanchez, E.; Moreno-Rey, C.; Real, L.M.; Ramirez-Lorca, R.; Saez, M.E. Identification of genetic factors associated with susceptibility to angiotensin-converting enzyme inhibitors-induced cough. *Pharmacogenet Genomics* **2011**, *21*, 10-17, doi:10.1097/FPC.0b013e328341041c.
100. Luo, J.Q.; He, F.Z.; Luo, Z.Y.; Wen, J.G.; Wang, L.Y.; Sun, N.L.; Tang, G.F.; Li, Q.; Guo, D.; Liu, Z.Q., et al. Rs495828 polymorphism of the ABO gene is a predictor of enalapril-induced cough in Chinese patients with essential hypertension. *Pharmacogenet Genomics* **2014**, *24*, 306-313, doi:10.1097/FPC.0000000000000050.
101. Mas, S.; Gasso, P.; Alvarez, S.; Ortiz, J.; Sotoca, J.M.; Francino, A.; Carne, X.; Lafuente, A. Pharmacogenetic predictors of angiotensin-converting enzyme inhibitor-induced cough: the role of ACE, ABO, and BDKRB2 genes. *Pharmacogenet Genomics* **2011**, *21*, 531-538, doi:10.1097/FPC.0b013e328348c6db.
102. Banegas, J.R.; Ruilope, L.M.; de la Sierra, A.; Vinyoles, E.; Gorostidi, M.; de la Cruz, J.J.; Ruiz-Hurtado, G.; Segura, J.; Rodriguez-Artalejo, F.; Williams, B. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. *N Engl J Med* **2018**, *378*, 1509-1520, doi:10.1056/NEJMoa1712231.
103. Banegas, J.R.; Ruilope, L.M.; Williams, B. Ambulatory Blood Pressure and Mortality. *N Engl J Med* **2018**, *379*, 1287-1288, doi:10.1056/NEJMc1809851.
104. El Rouby, N.; McDonough, C.W.; Gong, Y.; McClure, L.A.; Mitchell, B.D.; Horenstein, R.B.; Talbert, R.L.; Crawford, D.C.; Gitzendanner, M.A.; Takahashi, A., et al. Genome-wide

 doi:10.20944/preprints201905.0035.v1

association analysis of common genetic variants of resistant hypertension. *Pharmacogenomics J* **2018**, doi:10.1038/s41397-018-0049-x.

105. Gaddam, K.K.; Nishizaka, M.K.; Pratt-Ubunama, M.N.; Pimenta, E.; Aban, I.; Oparil, S.; Calhoun, D.A. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Archives of internal medicine* **2008**, *168*, 1159-1164, doi:10.1001/archinte.168.11.1159.
106. Yugar-Toledo, J.C.; Martin, J.F.; Krieger, J.E.; Pereira, A.C.; Demacq, C.; Coelho, O.R.; Pimenta, E.; Calhoun, D.A.; Junior, H.M. Gene variation in resistant hypertension: multilocus analysis of the angiotensin 1-converting enzyme, angiotensinogen, and endothelial nitric oxide synthase genes. *DNA Cell Biol* **2011**, *30*, 555-564, doi:10.1089/dna.2010.1156.
107. Shahin, M.H.; Gong, Y.; McDonough, C.W.; Rotroff, D.M.; Beitelshees, A.L.; Garrett, T.J.; Gums, J.G.; Motsinger-Reif, A.; Chapman, A.B.; Turner, S.T., et al. A Genetic Response Score for Hydrochlorothiazide Use: Insights From Genomics and Metabolomics Integration. *Hypertension* **2016**, *68*, 621-629, doi:10.1161/HYPERTENSIONAHA.116.07328.
108. Buckley, L.F.; Dixon, D.L.; Wohlford, G.F.t.; Wijesinghe, D.S.; Baker, W.L.; Van Tassell, B.W. Effect of intensive blood pressure control in patients with type 2 diabetes mellitus over 9 years of follow-up: A subgroup analysis of high-risk ACCORDION trial participants. *Diabetes Obes Metab* **2018**, *20*, 1499-1502, doi:10.1111/dom.13248.
109. Staessen, J.A.; Wang, J.G.; Thijs, L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* **2001**, *358*, 1305-1315, doi:10.1016/S0140-6736(01)06411-X.
110. Wright, J.T., Jr.; Williamson, J.D.; Whelton, P.K.; Snyder, J.K.; Sink, K.M.; Rocco, M.V.; Reboussin, D.M.; Rahman, M.; Oparil, S.; Lewis, C.E., et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* **2015**, *373*, 2103-2116, doi:10.1056/NEJMoa1511939.
111. Kelley, E.F.; Snyder, E.M.; Alkhatib, N.S.; Snyder, S.C.; Sprissler, R.; Olson, T.P.; Akre, M.K.; Abraham, I. Economic evaluation of a pharmacogenomic multi-gene panel test to optimize anti-hypertension therapy: simulation study. *J Med Econ* **2018**, 1-19, doi:10.1080/13696998.2018.1531011.