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Pharmacogenetics of Essential Hypertension

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1. Introduction

Hypertension is one of the most common chronic illnesses effecting more than 1 billion people worldwide and is a major risk factor for coronary artery disease and myocardial infarction, heart failure, stroke and renal failure. By the year 2025, the global prevalence of hypertension is projected to increase to 29.2% in adult population (Kearney et al., 2005). It is well established that reduction in blood pressure is associated with decreased cardiovascular morbidity and mortality (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). Despite the availability of several antihypertensive drugs which include thiazide diuretics, beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and calcium channel blockers, global estimates suggest that less than 35% of hypertensives are able to achieve their target systolic and diastolic blood pressure with these drugs (Thoenes et al., 2009). The current strategy of trial and error approach to the management of hypertension is suboptimal and alternative approaches for identifying the optimal antihypertensive regimen in a specific patient are needed. One potential approach for individualizing antihypertensive therapy is through the use of genetic information, or pharmacogenomics, to identify the most appropriate therapy for individual patients. Given the health burden associated with hypertension and the poor rates of BP control, hypertension pharmacogenomics holds great potential. Pharmacogenetics is the science that determines the efficiency and side effects of a medicine based on the genetic make-up of an individual (personalized medicine). Potential benefits of personalized medicines include prescription of drugs based on a patient's genetic profile versus trial and error, hence decreasing the likelihood of adverse reactions and maximizing effectiveness (Centre for Genetics Education, 2007). In the current review, we review genetic association of blood pressure lowering response to different drug classes of antihypertensive therapy in different ethnic populations.

2. Meta-analysis for pharmacogenetics of hypertension

In order to compile the current knowledge of pharmacogenetics of anti-hypertensive drugs, we searched PubMed using the MESH terms "Pharmacogenetics+hypertension, Genes + Hypertension, Blood pressure response + hypertension" in Pubmed limiting results to publications on studies in human adults. Similar searches were performed with names of specific antihypertensive drugs including Diuretics, Beta-blockers, ARB and ACE inhibitors. We further identified specific polymorphisms of genes of interest noted in earlier reviews

and performed additional PubMed searches based on these candidate genes. Studies on both healthy subjects and patients were included, and there was no time limit on duration of drug administration. Studies with both single and multiple drugs were included. Even if our information of interest was a small part of the study, it was included. Studies that only addressed the association of genetic variants/polymorphisms with hypertension and hypertension-induced end-organ damage but not with blood pressure alterations in response to anti-hypertensive drugs were not included. Reports related to experimental animals, or studies that used manipulated blood pressure (e.g. the attenuation of agonist-induced blood pressure increase) or were in languages other than English, or in which no specific drugs or drug classes were used (i.e. reports on therapy-resistant hypertension in general) were not included. Our aim was to collate the existing body of knowledge on common genetic polymorphisms and their relationship to blood pressure lowering response. We tried to remove bias in the selection of research articles by selecting maximum number of studies and from different ethnic groups. A summary of these findings is shown in the Table (1).

2.1 Diuretics

Diuretics are the first-line treatment of hypertension and Thiazides are most commonly prescribed diuretics. Thiazides inhibit Na^+/Cl^- cotransporter (NCC) in the renal distal convoluted tubule, resulting in decreased sodium re-absorption and increased sodium excretion, which leads to decreased extracellular fluid (ECF) and plasma volume. This volume loss results in diminished venous return, increased renin release, reduced cardiac output and decreased blood pressure (CONWAY & LAUWERS, 1960). Varied Blood pressure (BP) response to diuretics is observed in hypertensive patients. It has been proposed that genetic polymorphisms in several candidate genes such as the Angiotensin-Converting Enzyme (ACE), alpha-adducin (ADD1), G protein β_3 -subunit (GNB3) gene, angiotensinogen (AGT), angiotensin II receptor1 (AGTR1), etc. may influence blood pressure (BP) response to diuretic therapy (Arnett, Claas, & Glasser, 2006; Gerhard et al., 2008; C.-C. Huang et al., 2011; Luo, Y. Wang, et al., 2009; Sciarrone et al., 2003; Turner, Schwartz, Chapman, & Boerwinkle, 2001; D. Werner et al., 2008). ACE insertion/deletion (ACE I/D) polymorphism has been extensively studied for association with blood pressure lowering response to diuretics (Bozec et al., 2003; Nordestgaard et al., 2010; Scharplatz, Puhan, Steurer, & Bachmann, 2004; Su et al., 2007; Ueda, Meredith, Morton, Connell, & Elliott, 1998; Yu, Zhang, & G. Liu, 2003; Zhou, Wu, J.-Q. Liu, Liang, & G.-F. Liu, 2007); however conflicting results have been reported in different studies. Both, association / lack of association of ACE genotypes with blood pressure-lowering response to diuretics have been reported in different studies (Table). For example, a lack of association between ACE genotypes and adjusted mean difference in diastolic and systolic blood pressure in hypertensive patients on diuretics has been reported in Finnish (Suonsyrjä et al, 2009) and Swedish subjects (Schelleman et al 2006); whereas D allele was found to be associated with greater systolic blood pressure reduction in hypertensive Chinese patients on hydrochlorothiazide (HCTZ)(Jiang et al., 2007; Zhou et al., 2007). Sciarrone et al, 2003, on the other hand, showed that I allele of ACE (I/D) polymorphism was significantly associated with the largest mean blood pressure (MBP) decrease with HCTZ treatment. It has also been observed that response to thiazides may be gender specific (Frazier, S T Turner, G L Schwartz, A B Chapman, & E Boerwinkle, 0000; Zhou, Wu, J.-Q. Liu, Liang, & G.-F. Liu,

2007); for example, Schwartz et al (2002), reported that ACE II homozygosity in women and DD homozygosity in men was associated with the greatest BP lowering responses to HCTZ.

Two other genes, ADD1 and GNB3 genes have also been shown to influence the response to diuretics. α -Adducin is a ubiquitously expressed heterodimeric cytoskeleton protein that modulates a variety of cellular functions, including sodium transport. A genetic variant in ADD1, namely, Gly460Trp polymorphism has been shown to be associated with renal sodium reabsorption, salt-sensitive hypertension and response to diuretic therapy (Glorioso et al., 1999). However, the evidence remains inconsistent between studies and across populations. There are studies showing that use of diuretics in carriers of the 460Trp allele, significantly reduced the risk of cardiovascular outcomes and stroke when compared with other antihypertensive treatments (Cusi et al., 1997); however, negative studies, showing no significant association of ADD1 gene variants with diuretic mediated reduction in adverse cardiovascular events and stroke have also been published (Stephen T Turner, Arlene B Chapman, Gary L Schwartz, & Eric Boerwinkle, 2003). Genetics of Hypertension-Associated Treatment Study (GenHAT) also did not find Gly460Trp polymorphism to be an important modifier of cardiovascular risk. However, female carriers of variant allele treated with diuretics showed an increased risk of CHD, suggesting an interaction between gene variant and gender (Turner et al., 2008). ADD1 Gly460Trp polymorphism has also not been found to influence response to HCTZ in Finnish subjects (Suonsyrjä et al. 2009). A similar study on 5,979 hypertensive patients in USA showed a greater but non-significant association between Gly460Trp polymorphism and BP lowering effect of diuretics (Gerhard et al., 2008).

GNB3 gene, which encodes Beta subunit of Guanine nucleotide-binding protein G(I)/G(S)/G(T) which is associated with signal transduction across cell membranes, has been found to influence BP lowering response in hypertensive patients on diuretics; homozygous carriers of, GNB3 825TT (rs5443) genotype were found to show greater decline in blood pressure than homozygous CC patients in both white Caucasians (190) and African Americans (197) (Turner, Schwartz, Chapman, & Boerwinkle, 2001). In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a multicenter clinical trial conducted in the United States and Canada, minor C allele carriers of natriuretic peptide A gene (NPPA), a gene implicated in the control of extracellular fluid volume and electrolyte homeostasis, were found to respond significantly better to the diuretic chlorthalidone than carriers of other genotypes (Lynch et al., 2008). A recent study has reported that polymorphism in Renin gene may also modulate blood pressure lowering response of thiazide diuretics. In this study, it was seen that Renin CC genotype (rs11240688), Log PRA and baseline Systolic Blood Pressure (SBP), all contributed to the BP lowering response to Thiazide diuretics in non-diabetic hypertensive Taiwanese patients (Huang et al., 2011).

Several other candidate genes have been also examined for their association with BP lowering response to diuretics. For example, Werner et al., in 2008 have shown that CYP2C9*3 and SLCO1B1 c.521TC genotypes and female gender were significant and independent predictors of the pharmacokinetics of torasemide, a diuretic frequently used in treatment of hypertension in a small set of patients. Organic anion transporter (OAT) 1 and OAT3, encoded by a tightly linked gene pair, plays a key role in renal secretion of diuretics (Nozaki et al., 2007). An intergenic polymorphism between OAT1 and OAT3, rs10792367, has been investigated for BP response to the diuretic HCTZ. In a study on 1,106 Chinese

patients, no significant association was found even though it appeared to explain the inter individual variation in response to HCTZ (Han et al., 2011). The NEDD4L gene encodes E3 ubiquitin-protein ligase NEDD4-like enzyme, which reduces renal tubular expression of epithelial Na⁺ channel (ENaC) and is influenced by a functional rs4149601 G→A NEDD4L polymorphism. As diuretics inhibit renal sodium reabsorption, this polymorphism was studied for an effect on the diuretic efficacy. In Nordic Diltiazem Study (NORDIL) Sweden, the functional NEDD4L rs4149601 polymorphism was found to significantly influence the efficacy of diuretic-based antihypertensive treatment in hypertensive patients (Svensson-Färbom et al., 2011). Similar results have been reported in Chinese patients, where it was found that NEDD4L A-allele carriers showed greater blood pressure reduction than GG carriers with HCTZ (Luo et al., 2009). In yet another study, -344 C/T polymorphism in the CYP11b2 gene, which encodes aldosterone synthase was evaluated for BP response to diuretics in 340 individuals in Brazil; however no significant association between BP response and the polymorphism was observed (Lacchini et al., 2009). A genome wide association study (GWAS) to identify novel SNPs associated with the anti-hypertensive response to the diuretic, hydrochlorothiazide, has shown polymorphisms in two genes, LYZ (rs317689) and YEATS4 (rs315135) to be associated with Diastolic blood pressure lowering response in independent data set of African Americans and Caucasian white subjects (Turner et al., 2008).

Thus, till date, available literature remains inconclusive regarding predictive effect of genotypes on diuretic mediated antihypertensive response, however, with better study designs in future and replication of existing associations, it may be feasible to tailor diuretic therapy based on a patients' specific genetic make up.

2.2 β -blockers

β -Blockers are competitive antagonists of the β -adrenergic receptors, thereby modulating activities in this pathway (Reiter, 2004). Although β blockers are among the most widely prescribed of all drug classes for hypertension and various other cardiovascular diseases, β blocker therapy often produces variable responses among patients (Lindholm, Carlberg, & Samuelsson, 2005; Materson et al., 1993). Polymorphisms in various genes involved in sympathetic and renin-angiotensin-aldosterone systems (RAAS) have been investigated for association with variability in blood pressure lowering response to β -Blockers. Existing data suggests that polymorphisms in β 1-adrenoceptor gene (ADRB1), namely, Ser49Gly and Arg389Gly may influence blood pressure responses to β -blocker therapy (J. Liu et al., 2006; Aquilante et al., 2008). Homozygosity for ADRB1 Arg389 allele has been shown to be associated with greater decrease in SBP and DBP changes in Caucasians and Chinese hypertensive subjects and ADRB1 Ser49Arg389/Ser49Arg389 haplotype was found to be a predictor of a good SBP response to metoprolol, suggesting its predictability across races (Aquilante et al., 2008; J. Liu et al., 2006). In healthy volunteers with exercise induced heart rate increase, Arg389Arg genotype carriers were also found to show significantly greater reduction in systolic blood pressure than Gly389Gly carriers after 1 day of metoprolol treatment; however, plasma metoprolol concentrations were not significantly different between Arg389Arg and Gly389Gly genotypes 3 hours after metoprolol treatment, suggesting that differences in response were not due to variability in metoprolol pharmacokinetics (J Liu et al., 2003). However, no significant genotype based effects of

ADRB1 Ser49 and Arg389 polymorphism have been observed with dobutamine (Aquilante et al., 2008) or fluoxetine and paxetine in Caucasian Americans (Turner et al., 2008). ADRB1 Ser49Gly and Arg389Gly and ADRB2 Cys19Arg, Gly16Arg and Gln27Glu polymorphisms were also not found to significantly affect BP response to Atenolol (Filigheddu et al., 2010). In contrast, Pacanowski et al. (2008) found Ser49Gly and Arg389Gly to be significantly associated with response to atenolol in a study of 5,979 patients from 184 sites in the United States and Puerto Rico.

Three SNPs in the GNB3 gene, A3882C, G5249A and C825T have been found to have a significant effect on blood pressure response to atenolol in the female participants in Caucasian Americans (Filigheddu et al., 2010). Carvedilol is a non-selective α and β blocker that reduces the BP by blocking the binding of Norepinephrine to β 1- and β 2-adrenergic receptors (Stafylas & Sarafidis, 2008). Although polymorphism in CYP2D6 impact pharmacokinetics and pharmacodynamics of carvedilol, it has been shown to have no effect on the blood pressure response to the drug (Sehrt et al. 2011). However, ADRB2 Gln27 carriers were recently reported to show greater reduction in resting BP with carvedilol compared with Glu27carriers in Russian subjects (Teplakov et al., 2010).

The Glu41Leu polymorphism in GRK5 enhances desensitization of the β 1-adrenergic receptor and has been postulated to confer endogenous 'genetic β -blockade' and contribute to an attenuated response to β -blockers in black subjects. Thus GRK5 Gln41Leu variant could contribute to ethnicity base inter-individual variability in response to β -blockade between black and Caucasian individuals (Liggett et al., 2008). Kurnik et al. (2009), however, have observed that GRK5 Gln41Leu polymorphism did not contribute to the ethnic differences in sensitivity to atenolol among Black and Caucasian individuals.

NEDD4L polymorphism has been found to influence renal tubular expression of epithelial Na⁺ channel (EnaC) (Luo et al., 2009). Gene variants of Gs α (FokI polymorphism), and NEDD4L (rs4149601, G→A) polymorphisms have been investigated for a role in the blood pressure response to β blockers. Gs α genotype was not found to be a significant independent predictor of BP response (Jia et al., 1999); whereas NEDD4L rs4149601 polymorphism was shown to influence the efficacy of β -blockers in the NORDIL study (Svensson-Färbom et al., 2011).

Most of the existing data on pharmacogenetics of β - blockers remains inconclusive and further studies are needed to correlate the genotype -drug response to β - blockers in large populations from different ethnic communities so as to be an effective predictive tool.

2.3 ACE inhibitors

ACE inhibitors are one of the most commonly prescribed antihypertensives and block the production of angiotensin II by inhibiting ACE (encoded by the *ACE* gene), an enzyme that converts Angiotensin I to Angiotensin II (Cody, 1997). Polymorphisms in RAAS genes have been shown to influence antihypertensive response of ACE inhibitors, but the results have been contradictory and inconclusive (Lillvis & Lanfear, 2010). The commonly studied variations have been I/D polymorphism in the *ACE* gene, AGT Met235Thr polymorphism in the *AGT* gene and AGTR1- A1166C polymorphism (rs5186) (Roskopf & Michel, 2008; Scharplatz, Puhan, Steurer, & Bachmann, 2004). Both, D and I alleles of *ACE* I/D Polymorphism were shown to be associated with BP lowering response to ACE Inhibitors in

hypertensives in earlier studies (Ueda et al, 1998, Kurland et al, 2001); however, recent studies in larger cohorts have failed to replicate the BP response modulation by ACE inhibitors (Yu, Zhang, & Liu, 2003, D. K Arnett et al., 2005, F. Filigheddu et al., 2008). Recently, another ACE SNP, rs4343, which is located near the ACE I/D and is in linkage disequilibrium with it, has been reported to be strongly associated with BP response to ACE inhibitors in a Genome Wide Association Study (C-M Chung et al., 2010). However this association could not be reproduced in the large randomized placebo controlled EUROPA trial (Brugts et al., 2010).

Besides ACE gene variants, 235T allele of AGT (M235T) gene has also been found to be associated with BP response to ACE inhibitors in several studies (Table). However, a recent study with larger sample size did not show any significant association of this variant with BP response to β blockers (Schelleman et al., 2007). Su et al., 2007 have reported the association of other AGT SNPs with BP response to benazepril, an ACE Inhibitor. These authors also found a significant association of AGT gene polymorphisms, C11537A (rs7079), rs2638362 (C/T) and rs2640543 (G/A) with BP response to ACE inhibitors (Su et al., 2007). AGTR1, which is an important receptor in the RAAS system and plays a crucial role in BP control (Atlas, 2007), is an important candidate for study of genetic variation-pharmacological associations. Its genetic variant, A1166C has been extensively evaluated for an effect on BP lowering by ACE inhibitors (Redon, Luque-Otero, Martell, & Chaves, 2004; Scharplatz et al., 2004) but recent studies have not found any significant effect of this variant with BP lowering ability of ACE inhibitors (Brunner et al., 2007; Filigheddu et al., 2008; Konoshita, 2011; Nordestgaard et al., 2010; Redon, Luque-Otero, Martell, & Chaves, 2004; H. Yu et al., 2009). Besides these commonly studied polymorphisms, the bradykinin B1 receptor gene (BDKRB1) SNP (rs12050217) and the ABO gene polymorphisms (rs495828 and rs8176746) have been also found to be significantly associated with blood pressure response to ACE inhibitors (Brugts et al., 2010; Chung et al., 2010).

2.4 Angiotensin Receptor Blockers (ARB)

Angiotensin receptor blockers (ARBs), also known as sartans, block the activation of angiotensin type 1 receptors and have a recognized role in the treatment of blood pressure. Studies on ARB pharmacogenetics have commonly focused on genes of RAAS system. A small-scale study investigated the role of AGTR1- A1166C polymorphism in patients with heart failure who were taking ARB (candesartan) in addition to the ACE inhibitor for BP control. This study observed that AGTR1 A1166C polymorphism significantly influenced the BP response to candesartan (de Denu et al., 2008). However, studies on larger cohorts could not replicate association of AGTR1 A1166C and C573T polymorphisms on the efficacy of ARBs (Konoshita, 2011; Nordestgaard et al., 2010). Variants of other RAAS genes such as ACE (I/D), AGT (M235T) and AT2 variants have not been found to be significantly associated with the action of ARB in BP lowering (Konoshita, 2011; Nordestgaard et al., 2010). A recent study has reported that C-5312T polymorphism of the renin gene (REN) was associated with pharmacogenetics of ARBs (Konoshita, 2011). Additionally, some pilot studies have been conducted on small sample sizes (n=31 to 49) that show significant associations but they need to be reproduced in larger cohorts. In one of these small-scale study, for example, Cytochrome P450 CYP2C9 enzyme (CYP2C9) that metabolizes angiotensin II type 1 (AT (1)) receptor antagonists losartan and irbesartan, has been found to be associated with the DBP response to irbesartan (Hallberg et al., 2002). In another study, AGTR1 5245 TT genotype was found to be associated with plasma concentrations of irbesartan, a specific angiotensin II type 1 receptor

(AGTR1) antagonist and the blood pressure response in hypertensive patients (Kurland et al., 2008). However, these results can't be considered reliable on account of the small sample sizes and need to be validated with larger sample sizes.

2.5 Calcium channel blockers

The large-conductance calcium and voltage-dependent potassium (BK) channel found in vascular smooth muscle is comprised of pore-forming- α and regulatory- β 1 subunits (Fernández-Fernández et al., 2004). The BK channel, particularly the β 1 subunit, functions in a negative feedback mechanism to enhance calcium sensitivity, decrease cell excitability, and limit smooth muscle contraction (Fernández-Fernández et al., 2004). Calcium channels are present in the smooth muscles that line the blood vessels. By relaxing these smooth muscles, calcium channel blockers dilate the blood vessels and reduce the BP (Jun et al., 2010). Calcium channel blockers are commonly used in the treatment of hypertension and angina but the response is widely variable (Nguyen, Parker, Noujedehi, Sullivan, & J A Johnson, 2000). This variability may be best explained by genetic variation and identifying the exact cause of this varied response to calcium channel blockers is important in personalizing treatment for hypertension. The gene that encodes the β 1 subunit of the BK channel is KCNMB1, which is likely to carry polymorphisms, which affect the efficacy of calcium channel blockers. Glu65Lys and Val110Leu are the two commonly studied polymorphisms in this gene (Brunner et al., 2007; Plüger et al., 2000). In the INVEST-GENE study, BP response to Verapamil SR was not found to differ by KCNMB1 genotypes. However, individuals with Lys65 allele were found to achieve BP control earlier and were found to be less likely to require multiple drugs for BP control than those with Glu65Glu genotype (Beitelshees et al., 2007). In another analysis of the INVEST GENE study, Verapamil efficacy was investigated for association with the SNPs of endothelial NO synthase (eNOS) gene. Nitric Oxide (NO), the product of NOS gene is a critical mediator of vascular tone and also has antiplatelet, antiproliferative and antimitogenic effect and eNOS activity is important in cardiovascular outcomes and response to treatment. Two commonly studied SNPs are NOS3 -786T>C in promoter region, which reduces gene expression (Cattaruzza et al., 2004; Iwai et al., 2003; Nakayama et al., 1999) and a nonsynonymous SNP (894G>T), which increases its susceptibility to proteolytic cleavage (Tesauro et al., 2000), reducing NO bioavailability (Leeson et al., 2002; Persu et al., 2002; Savvidou, Vallance, Nicolaides, & Hingorani, 2001). The -786T>C genotype was shown to be significantly associated with response to Verapamil; -786C allele carriers showed the greatest reduction in SBP/DBP. However, eNOS 894G>T genotypes were not found to significantly affect the BP response (M. A. Pacanowski, Zineh, Rhonda M. Cooper-DeHoff, Carl J. Pepine, & Julie A. Johnson, 2009). Amlodipine, a dihydropyridine (DHP) class calcium channel blocker is another drug routinely prescribed for BP control. In the ALLHAT study conducted in the USA and Canada, NPPA T2238C allele was found to be significantly associated with the action of this drug. It was seen that TT allele carriers responded better to calcium channel blockers (Lynch et al., 2008). However, in order to be useful in clinical settings, these studies need to be conducted in wider regions of the world covering more ethnic populations.

3. Conclusion and future perspectives

Despite the availability of several effective anti hypertensive drug therapies, optimal control of blood pressure remains elusive in a large set of patients. Pharmacogenetics of

antihypertensive therapy has the potential to tailor therapy according to patients genetic make up as is evidenced by the above Meta analysis. However, prediction of the right drug for optimum BP control requires large-scale studies on ethnically diverse populations. Most of the studies till date have focused on candidate genes and sample size has ben small. Individual groups were only able to detect small effects in their individual population but collaborating with other groups conducting GWAS and also focusing on relevant pathways will make this more tractable approach and lead to successful clinical translation. Replicating these findings across multiple ethnic populations will also be an be an important aspect of personalizing treatment on genetic basis and increased international collaboration among hypertension pharmacogenomics investigators will be very important to achieve this goal. Additionally whole genome mapping of hypertension and blood pressure traits and understanding the pharmacogenetics of current drugs will enable the discovery of new drug targets in future.

Drug Class	Drug	Area	Ethnicity	Sample size, N	Genetic variants	Significant difference?	Reference
Diuretic	Hydrochloro-thiazide	USA	Non-Hispanic white (50%) Non-Hispanic Black (50%)	389	LYZ (rs317689) YEATS4 (rs315135)	Yes Yes	(Turner et al., 2008)
		USA	White Caucasian (190) African American (197)	387	GNB3 C825T (rs5443)	Yes	(Turner et al., 2001)
	Chlorthalidone	USA		13,860	NPPA T2238C	Yes	(Lynch et al., 2008)
	Hydrochloro-thiazide	Taiwan	Taiwanese	90	Renin (rs11240688)	Yes	(C. -C. Huang et al., 2011)
	Hydrochloro-thiazide	Netherlands	Dutch	613	ADD1 Gly460Trp (rs4961)	No	(van Wieren-de Wijer et al., 2009)
β Blockers	Dobutamine	USA	White	163	ADRB1 (Ser49Gly)	No	(Aquilante et al., 2008)
					ADRB1 (Arg389Gly)-rs1801253	No	
					ADRB2 (Arg16Gly)	No	
					ADRB2 (Gln27Glu)	No	
	Fluoxetine and paroxetine	USA	White	122	ADRB1 (Arg389Gly)-rs1801253	Yes	(Turner, Bailey, Fridley, Chapman, Schwartz, Chai, Sicotte, Kocher, Rodin, & Boerwinkle, 2008b)
	Carvedilol	USA	Caucasian	110	ADRB2 (Gln27Glu)	Yes	(Sehrt, Meineke, Tzvetkov, Gültepe, &
					CYP2D6	No	

Drug Class	Drug	Area	Ethnicity	Sample size, N	Genetic variants	Significant difference?	Reference
							Brockmüller, 2011)
	Atenolol	USA	African Americans (69) and Caucasian White (85)	151	GRK5-Leu41 (rs17098707)	No	(Kurnik et al., 2009)
	Bisoprolol	Finland	Finnish	233	ADRB1 (Ser49Gly)(145A>G)-rs1801252	No	(Suonsyrjä et al., 2010)
					ADRB1 (Arg389Gly)-rs1801253	No	
	Amlodipine	USA	Multi-ethnic	8174	T2238C	Yes	(Lynch et al., 2008)
	Metoprolol	China	Chinese	61	ADRB1 (Ser49Gly)(145A>G)-rs1801252	Yes	(J. Liu et al., 2003)
					ADRB1 (Arg389Gly)-rs1801253	Yes	
	Atenolol	Italy	Italians	1112	ADRB1 (Arg389Gly)	No	(Fabiana Filigheddu et al., 2010)
					ADRB1 (Ser49Gly)-(145A>G)-rs1801252		
					ADRB2 (Cys19Arg)		
					ADRB2 (Gly16Arg)		
					ADRB2 (Gln27Glu)		
					GNB3 (A3882C)		
					GNB3 (G5249A)		
					GNB3 (C825T)		
	Trandolapril and/or Atenolol	USA and Puerto Rico	Multiethnic	5,979	ADRB1 Ser49Gly (145A>G)-rs1801252	Yes	(Pacanowski et al., 2008)
					ADRB1 Arg389Gly (1165C>G)-rs1801253	Yes	
ACEI	Imidapril or benazepril	China	Chinese	517	ACE (I/D)	No	(Yu, Zhang, & Liu, 2003)
	Imidapril or benazepril	China	Chinese	501	AGT (M235T)	No	(H. Yu et al., 2005)
	Lisinopril	USA	White Caucasians (61%)	7,528	ACE (I/D)	No	(D. K Arnett et al., 2005)
			African Americans (35%)				
	Benazepril	China	Chinese	1,447	AGT (rs7079 (C/T))	Yes	(Su et al., 2007)
					AT1 (multi loci, H2 & H3)	Yes	
					AT2 (multi loci)	No	
	Trandolapril	USA	White (35%)	551	AT1 (A1166C)	No	(Brunner et al., 2007)
			Hispanic (44%)				
	Captopril	China	Chinese	624	ACE2 (rs2106809)	Yes	(Fan et al.,

Drug Class	Drug	Area	Ethnicity	Sample size, N	Genetic variants	Significant difference?	Reference
	Fosinopril	USA	White	191	ACE (I/D)	No	2007)
					AGT (A-6G)	No	(F. Filigheddu et al., 2008)
					AT1 (A1166C)	No	
	Imidapril benazepril	China	Chinese	509	AT1 (A1166C)	No	(H. Yu et al., 2009)
	Lisinopril	USA	White non-Hispanic (47%)	30,076	FGB-455	Yes	(Lynch et al., 2009)
	ACEI	Taiwan	Taiwanese	623	ACE (rs4343)	Yes	(Chung et al., 2010)
					ABO (rs495828)	Yes	
					ABO (rs8176746)	Yes	
	Perindopril	Europe	Caucasians	8907	AGTR1 (rs275651)	Yes	(Brugts, Boersma, & Simoons, 2010)
					AGTR1 (rs5182)		
					BDKRB1 (rs12050217)		
	Enalapril	Europe	Caucasians	98	AGT (M235T)	Yes	(Bozec et al., 2003)
ARB	Telmisartan	Spain	Spanish	206	AGT (A-6G)	No	(Redon, Luque-Otero, Martell, & Chaves, 2004)
					ACE (I/D)		
					AT1 (A1166C)		
					AT1 (C573T)		
	Valsartan	Japan	Japanese	231	ACE (I/D)	No	(Konoshita, 2011)
					AGT (M235T)	No	
					AT1 (A1166C)	No	
					AT2 (C3123A)	No	
					REN (C-5312T)	Yes	
	Losartan	Scandinavia	White (92%)	1,774	ACE (I/D)	No	(Nordestgaard et al., 2010)
					AGT (M235T)	No	
					AT1 (A1166C)	No	
Calcium channel blockers	Verapamil SR	USA	Hispanics, White Caucasians and Afro Americans	5979	KCNMB1 (Glu65Lys)	No	(Beitelshees et al., 2007)
					KCNMB1 (Val110Leu)	No	
	Verapamil SR	USA	Hispanics, White Caucasians and Afro Americans	1025	NOS3 (-786T>C)(rs2070744)	Yes	(M. Pacanowski et al., 2008)
					NOS3 Glu298>Asp (rs1799983)	No	
	Amlodipine	USA and Canada	Multi-ethnic	8174	NPPA (T2238C)	Yes	(Lynch et al., 2008)

Table 1.

4. References

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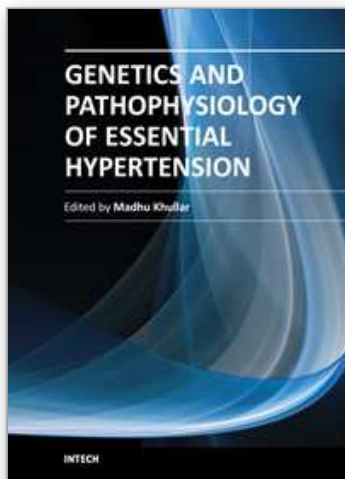
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This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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