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A Hypertension Gene: Are We There Yet?

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Cardiovascular diseases are the leading cause of death worldwide. Essential hypertension is a major risk factor for the development of other cardiovascular diseases and is caused by a combination of environmental and genetic factors, with up to 50% of blood pressure variance currently attributed to an individual's genetic makeup. By studying genes that cause monogenic forms of hypertension and pathways relevant to blood pressure control, a number of polymorphisms have been identified that increase an individual's risk of developing high blood pressure. We report on candidate gene association studies and genome-wide association studies that have been performed to date in the field of hypertension research. It is becoming clear that for the majority of people there is no single gene polymorphism that causes hypertension, but rather a number of common genetic variants, each having a small effect. Using pharmacogenomics to personalize the treatment of hypertension holds promise for achieving and sustaining normotensive pressures quickly, while minimizing the risk of adverse reactions and unwanted side-effects. This will decrease the risk of stroke and myocardial infarction in individuals and lead to a reduced burden of disease upon society as a whole.

■ **Keywords:** hypertension, blood pressure, genetics, association studies, pharmacogenomics

Cardiovascular diseases are the leading cause of death worldwide, and by 2030 an estimated 23.6 million people will die from cardiovascular diseases each year (World Health Organization, 2011). Cardiovascular diseases affect the heart and blood vessels and include heart attacks and stroke. A combination of an individual's genes and the environment contribute to the development of cardiovascular diseases, with the greatest risk factors being high blood pressure and high serum cholesterol levels (Whitworth, 2003).

Blood pressure is a continuously distributed variable, and no rigidly defined pressure threshold distinguishes high risk from low risk. However, as blood pressure levels increase, so does the risk of complications (Reckelhoff, 2000). An increase in systolic blood pressure by 20 mmHg or in diastolic blood pressure by 10 mmHg doubles the number of fatal strokes in the 40–69 year age group (Lewington et al., 2002). A cut-off point distinguishing health from disease has therefore been defined as sustained systolic blood pressure equal to or above 140 mmHg and/or sustained diastolic blood pressure equal to or above 90 mmHg (O'Donnell et al., 1998).

Hypertension is classified into essential and secondary hypertension. Essential hypertension is idiopathic, and accounts for approximately 95% of hypertensive patients. Secondary hypertension affects the remaining 5%, and has an identifiable cause, such as renal or adrenal disease (Williams, 2007). The symptoms of hypertension are usually minor. The patient may experience headache, although the vast majority of patients will remain asymptomatic until the disease is quite progressed (Williams, 2007). Undiagnosed asymptomatic hypertension can have devastating consequences for the patient, inducing arteriosclerosis, kidney damage, and 'wet' macular degeneration (Wong & Mitchell, 2007; Facemire et al., 2009). Hypertension can also lead to cardiac hypertrophy, heart failure, and aortic dissection due to structural changes in the heart muscle and in blood vessel walls (O'Donnell et al., 1998; Williams, 2007). As a complex, multifactorial disease, the risk factors for hypertension include age, body mass index (BMI), positive family history, diet, tobacco use and genetic factors (Tamaki et al., 2002; Dzau et al., 2006; Yi et al., 2006).

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Common genetic polymorphisms appear to confer a modestly increased risk for cardiovascular disease (Jeunemaitre et al., 1992). Familial analysis using twins and other family members indicates that 30% of blood pressure variance is due to environmental factors, and 40 to 50% of variance is due to genetic factors (O'Donnell et al., 1998). Genetic linkage studies in families have identified a number of genes that are responsible for rarer Mendelian forms of hypertension (Wilson et al., 2001). All of the known monogenic forms of hypertension alter the net sodium reabsorption in the distal tubule of the nephron, causing fluid retention and fluid overload (Luft, 2004). These genes have provided good candidates for the study of essential hypertension, and have helped to determine some of the molecular pathways involved in blood pressure control (Tobin et al., 2008). Candidate gene studies and genome-wide association studies have been applied to the field of hypertension research, identifying polymorphisms that increase the risk of developing high blood pressure. While these studies have had some success in identifying variants that increase an individual's risk of developing disease, the field of pharmacogenomics shows the greatest promise in reducing the burden of disease by tailoring hypertensive therapies to individual patients based on their gene sequences.

Candidate Gene Association Studies

Numerous candidate gene association studies have been published with an aim of identifying genes that increase an individual's risk of developing high blood pressure. These studies have focused on variation in genes involved in the renin-angiotensin-aldosterone system (RAAS), renal sodium transport, adrenergic pathways, vascular-related genes, or metabolism-related genes. Table 1 lists a number of genes that have been investigated with regard to association with blood pressure.

The most comprehensively studied pathway is the RAAS, and many of the anti-hypertensive drugs available today are inhibitors of this system. The RAAS controls the balance of salt and water in the body (reviewed by Oparil & Haber, 1974a, 1974b). Genes within the RAAS, namely *ACE*, *AGT,* and *AGTR1*, have formed the basis of a number of candidate gene studies, aiming to identify genetic variants that increase an individual's risk of developing hypertension.

Polymorphisms within the *ACE* gene have been shown to increase the risk of essential hypertension. One of the most intensively studied polymorphisms, the insertion/deletion (I/D) polymorphism, consists of a 287bp DNA sequence in intron 16 of the *ACE* gene (Rigat et al., 1990). The association of the I/D polymorphism in the *ACE* gene with hypertension is controversial. A study by Zee et al. (1992) found a positive association between the insertion *ACE* polymorphism and hypertension, and patients with a family history of hypertension were found to have a higher frequency of the insertion allele (Zee et al., 1992). However, in 1998, O'Donnell et al., using data collected from the Framingham Heart Study, found that the deletion polymorphism is associated with hypertension in men, but not in women (O'Donnell et al., 1998). To add to the controversy, studies completed in the Dutch and Greek populations have failed to find any association between the *ACE* I/D allele and hypertension (Schmidt et al., 1993; Vassilikioti et al., 1996). As the *ACE* I/D polymorphism is intronic, the mechanism of *ACE* overexpression in subjects with the genotype is possibly the result of tight linkage to another locus involved in the regulation of *ACE* gene expression (Davis & Roberts, 1997).

Of the multiple single nucleotide polymorphisms (SNPs) in genes involved in the RAAS, one common polymorphism in the angiotensinogen gene (*AGT*) is a T-to-C substitution in exon 2, position 704, resulting in a methionine-to-threonine substitution. This SNP is associated with increased plasma angiotensinogen levels and hypertension. An A to C substitution at position 1166 in the *AGTR1* gene was also found at increased frequency in patients with hypertension, possibly due to aortic rigidity (Bonnardeaux et al., 1994; Benetos et al., 1996).

A study by Tobin et al., (2008) investigated candidate genes that had been shown to cause monogenic hypertension in a normal population (Tobin et al., 2008). Common variants in 11 candidate genes were genotyped in 2037 individuals. Polymorphisms in *KCNJ1, CASR, NR3C2, SCNN1B* and *SCNN1G* were found to be associated with systolic and diastolic blood pressure. A further study investigating 160 candidate genes for association with essential hypertension using the Affymetrix 500K chip found no SNPs were significantly associated with blood pressure after P-value corrections. Twelve SNPs in seven genes (*ADRA2A*, *LEP*, *LEPR*, *PTGER3*, *SLC4A1*, *SLC4A2* and *SLC8A1*) were found to exhibit considerable associations with high blood pressure, however the associations could not be replicated in other populations (Sober et al., 2009).

Despite the large number of reported associations that have been identified in hypertension research, candidate gene association studies have only been able to explain a small fraction of the variation seen in blood pressure, and the results have been inconsistent, largely due to an inability to replicate these findings amongst different populations. This method is limited, as it relies on prior knowledge of disease mechanisms and precludes the discovery of unknown pathways. Genome-wide association studies allow an unbiased assessment of all genes in the genome, and have enabled the identification of common variants associated with common disease and traits.

Genome-Wide Association Studies

A number of genome-wide association studies (GWAS) have been undertaken to identify loci associated with

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TABLE 1

Candidate Genes That Have Been Associated With Essential Hypertension

System/pathway	Gene	Symbol	Reference
RAAS	Angiotensin 1 converting enzyme	*ACE*	Fan et al., 2007
	Angiotensin 1 converting enzyme 2	*ACE2*	Song et al., 2011
	Angiotensinogen	*AGT*	Rodriguez-Perez et al., 2001
	Angiotensin II receptor type I	*AGTR1*	Jiang, Zhao et al., 2001
	Aldosterone synthase	*CYP11B2*	Cheng & Xu, 2009
	11-β-hydroxylase	*CYP11B1*	Keavney et al., 2005
	Mineralocorticoid receptor	*NR3C2*	Song, et al., 2011
	Renin	*REN*	B. Sun et al., 2011
	Chymase 1	*CMA1*	Song, et al., 2011
	Hydroxy-δ-5-steroid dehydrogenase	*HSD3B1*	Shimodaira et al., 2010
Na+ Transport/Volume	α-adducin	*ADD1*	J. G. Wang et al., 2002
	β-adducin	*ADD2*	J. G. Wang, et al., 2002
	Protein kinase lysine deficient 1	*WNK1*	Putku et al., 2011
	Protein kinase lysine deficient 4	*WNK4*	Z. J. Sun et al., 2009
	Solute carrier family 4, member 1	*SLC4A1*	Sober, et al., 2009
	Solute carrier family 4, member 2	*SLC4A2*	Sober, et al., 2009
	Solute carrier family 6, member 9	*SLC6A9*	Ueno et al., 2009
	Solute carrier family 8, member 1	*SLC8A1*	Sober, et al., 2009
	Solute carrier family 12, member 1	*SLC12A1*	Acuna et al., 2011
	Solute carrier family 12, member 3	*SLC12A3*	Acuna, et al., 2011
	Natriuretic peptide precursor A	*NPPA*	Conen et al., 2009
	Natriuretic peptide precursor B	*NPPB*	Kosuge et al., 2007
	G Protein β3 subunit	*GNB3*	Cabadak et al., 2011
	Potassium inwardly-rectifying channel	*KCNJ1*	Tobin, et al., 2008
	Sodium channel, non-voltage-gated 1	*SCNN1B*	Tobin, et al., 2008
	Sodium channel, non-voltage-gated 1	*SCNN1G*	Tobin, et al., 2008
Vascular	Endothelial nitric oxide synthase	*eNOS*	Jachymova et al., 2001
	Endothelin 1	*ET1*	Asai et al., 2001
	Endothelin receptor type A	*EDNRA*	Benjafield et al., 2003
	Elastin microfibril interfacer 1	*EMILIN1*	Shimodaira et al., 2010
	Protein tyrosine kinase 2β	*PTK2B*	Kamide,et al., 2007
Adrenergic	β2-adrenergic receptor	*ADRB2*	Lou et al., 2011
	α1A-adrenergic receptor	*ADRA1A*	Gu, Ge, et al., 2006
	α2A-adrenergic receptor	*ADRA2A*	Sober, et al., 2009
	Regulator of G-protein Signaling 2	*RGS2*	Riddle et al., 2006
	G protein–coupled receptor kinase 4	*GRK4*	Gu, Su, et al., 2006
	Catecholamine-O-methyltransferase	*COMT*	Kamide et al., 2007
	Prostaglandin E receptor 3	*PTGER3*	Sober, et al., 2009
	Acyl-CoA dehydrogenase	*ACADSB*	Kamide et al., 2007
Other	Phenylethanolamine N-methyltransferase	*PNMT*	Cui et al., 2003
	Fatty acid binding protein 3	*FABP3*	Ueno et al., 2008
	Arachidonate 12-lipoxygenase	*ALOX12*	Quintana et al., 2006
	Methylenetetrahydrofolate reductase	*MTHFR*	Conen, et al., 2009
	Heme oxygenase-1	*HMOX1*	Lin et al., 2011
	Cytochrome P450 family 4	*CYP4A11*	Fu et al., 2008
	Cytochrome P450, family 2	*CYP2J2*	Wu et al., 2007
	Catalase	*CAT*	Zhou et al., 2005
	Aromatase	*CYP19A1*	Shimodaira et al., 2008
	Tyrosine hydroxylase	*TH*	Gu, Su, et al., 2006
	Renalase	*RNLS*	Q. Zhao et al., 2007
	Transforming growth factor β	*TGFB1*	Yan-Yan, 2011
	Tumor necrosis factor receptor superfamily, member 4	*TNFRSF4*	Mashimo et al., 2008
	Kininogen 1	*KNG1*	W. Zhao et al., 2009
	Calcium sensing receptor	*CASR*	Tobin, et al., 2008
	Interleukin-10	*IL10*	Timasheva et al., 2008
	Leptin	*LEP*	Sober, et al., 2009
	Leptin receptor	*LEPR*	Sober, et al., 2009

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hypertension and blood pressure control. However, few have identified loci that achieve genome-wide significance levels ($P < 5 \times 10^{-8}$). This is thought to be the result of blood pressure variability being due to multiple variants with small effects.

The Wellcome Trust Case Control Consortium reported the first GWAS for hypertension in 2007, involving 2,000 cases of essential hypertension and 3,000 controls (WTCCC, 2007). Although no single SNP reached genome-wide significance, a number of variants with moderate association ($5 \times 10^{-7} < P < 1 \times 10^{-5}$) were identified. The top six variants most significantly associated with hypertension were later investigated in 11,433 hypertensive individuals from the Family Blood Pressure Program. Only one of the six SNPs, rs1937506, was identified as being potentially associated with both systolic and diastolic blood pressure in individuals of a European origin and those of a Hispanic origin. The effect of the variant on systolic and diastolic blood pressure was large but, interestingly, in opposite directions in the European and Hispanic populations (Ehret et al., 2008).

A GWAS of 1,644 German individuals from the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) S3 cohort similarly did not reveal any variants that were associated with blood pressure or hypertension at genome-wide significance (Org et al., 2009). Eighty SNPs exhibited strong association with blood pressure and hypertension ($P < 5.5 \times 10^{-5}$), and attempts to confirm these associations were undertaken in two independent European populations (KORA S4 cohort n = 1830 and HYPEST n = 1823). A single variant, rs11646213 (T/A), upstream of the *CDH13* gene at 16q23.3, was associated with diastolic blood pressure ($P = 5.55 \times 10^{-5}$) and hypertension ($P = 5.30 \times 10^{-8}$) in both populations. *CDH13* encodes for an adhesion glycoprotein T-cadherin, a regulator of vascular wall remodeling and angiogenesis. Carriers of the minor allele A had a decreased risk of hypertension (Org et al., 2009).

Meta-analysis of multiple studies with large total sample sizes has the potential to detect variants that have modest effects. To date, only two GWAS on blood pressure and hypertension have identified loci associated with blood pressure at genome-wide significance levels. Both these studies, Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) and Global BPgen, were performed in large consortiums using blood pressure as a continuous trait and were published simultaneously (Levy et al., 2009; Newton-Cheh et al., 2009). The Global BPgen GWAS genotyped 34,433 individuals from 13 prospective and 4 case-control type studies, and identified 11 loci for systolic blood pressure and 15 loci for diastolic blood pressure with a $P < 1 \times 10^{-5}$, with two loci attaining genome-wide significance. These results were then replicated in 71,225 Europeans and 12,889 individuals of Indian Asian ancestry. Meta-analysis of the GWAS and the replication results identified genome-wide significant association at eight loci, three associated with systolic blood pressure, and five associated with diastolic blood pressure (Table 2). Each of the eight associated loci were examined for associations to hypertension, and were found to be associated with odds of hypertension in the same direction as the effect of the blood pressure trait (Newton-Cheh et al., 2009). The CHARGE consortium group consisted of 29,136 individuals from six different cohorts of European ancestry. Initial analysis within the cohort identified 13 SNPs for systolic blood pressure, 20 for diastolic blood pressure and 10 for hypertension status at $P < 4 \times 10^{-7}$ (Levy et al., 2009). Combined meta-analysis of CHARGE and Global BPgen for the top ten CHARGE SNPs for systolic and diastolic blood pressure and hypertension identified four genome-wide significant associations for systolic blood pressure, six for diastolic blood pressure and one for hypertension (Table 2; Levy et al., 2009; Newton-Cheh, et al., 2009).

Based on the findings from the CHARGE and Global BPgen GWAS, replication studies have been attempted in a Japanese population, a Korean population, and the Women's Genome Health Study population. The Japanese study investigated 27 unique loci that had been reported by the CHARGE and Global BPgen GWAS (Levy, et al., 2009; Newton-Cheh et al., 2009) to be associated with blood pressure, and found significant associations for seven loci (Takeuchi et al., 2010). Similarly, the Korean Association REsource (KARE) study (n = 8,512) examined 27 SNPs and showed replication for four loci (Hong et al., 2010). The Women's Genome Health Study (n = 23,019) targeted 18 SNPs with genome-wide significance and an additional 13 with suggestive associations from previously established GWAS. They were able to replicate 13 of the 18 significant SNPs and three of the 13 suggestive SNPs. In addition, meta-analysis of the Women's Genome Health Study and CHARGE or Global BPgen revealed a novel blood pressure locus with genome-wide significance (Ho et al., 2011).

The majority of GWAS for hypertension or blood pressure have been performed in populations of European ancestry, with only a small number of studies investigating blood pressure traits in non-European populations. In addition to the Japanese and Korean replication studies mentioned previously, a study in Han Chinese looking at young-onset hypertension failed to identify genome-wide associated loci (Yang et al., 2009). A GWAS for blood pressure in 509 hypertensive and 508 normotensive African Americans reported multiple SNPs reaching genome-wide significance for systolic blood pressure in or near the genes *PMS1, SLC24A4, YWHAZ, IPO7* and *CACANA1H*. An attempt to replicate these results in an independent population of West Africans failed (Adeyemo et al., 2009). Identification of blood pressure variants in minority populations has been challenging due to the reduced coverage of

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TABLE 2

Top Results for GWAS in Blood Pressure and Hypertension

Study	SNP	Loci	Nearby genes	Trait / P-value	Reference
CHARGE	rs17367504	1p36		SBP $1x10^{-5}$	Newton-Cheh et al., 2009
	rs11191548	10q24		SBP $3x10^{-7}$	
	rs12946454	17q21		SBP $4x10^{-6}$	
	rs16998073	4q21	*PRDM8/FGF5*	DBP $7x10^{-9}$	
	rs1530440	10q21	Intron *c10orf107*	DBP $3x10^{-6}$	
	rs653178	12q24	*SH2B3*	DBP $1x10^{-7}$	
	rs1378942	15q24	Intron *CSK*	DBP $6x10^{-8}$	
	rs16948048	17q21	*ZNF652*	DBP $6x10^{-6}$	
Global BPgen	rs1004467	10q24	*CYP17A1*	SBP $2x10^{-6}$	Levy et al., 2009
	rs381815	11p15	*PLEKHA7*	SBP $6x10^{-7}$	
	rs2681492	12q21	*ATP2B1*	SBP $3x10^{-11}$	
	rs2681472	12q21	*ATP2B1*	DBP $4x10^{-8}$	
	rs3184504	12q24	*SH2B3*	DBP $2x10^{-8}$	
	rs9815354	3p22	*ULK4*	DBP $8x10^{-7}$	
	rs11014166	10p12	*CACNB2*	DBP $9x10^{-7}$	
	rs2384550	12q24	*TBX3-TBX5*	DBP $1x10^{-7}$	
	rs6495122	15q24	*CSK – ULK3*	DBP $8x10^{-7}$	
Women's Genome Health Study	rs2898290	8p22	*BLK-GATA4*	SBP $3x10^{-8}$	Ho et al., 2011
Wellcome Trust Case Consortium	rs1937506	13q21		HT $5x10^{-5}$	Ehret et al., 2008; WTCCC, 2007
KORA	rs11646213	16q23.3	*CDH13*	HT $5.30x10^{-8}$	Org et al., 2009
Japanese Cohort	rs880315	1p36	*CASZ1*	DBP $5x10^{-12}$	Takeuchi et al., 2010
	rs17367504	1p36	*MTHFR*	DBP 0.05	
	rs155524	3p21	*ITGA9*	SBP 0.05	
	rs12413409	10q24	*CYP17A1-CNNM2*	SBP $1x10^{-14}$	
	rs2681472	12q21	*ATP2B1*	SBP $1.5x10^{-7}$	
	rs1378942	15q24	*CSK-ULK3*	DBP 0.009	
African American Cohort	rs5743185	2q31	*PMS1*	SBP $2x10^{-11}$	Adeyemo et al., 2009
	rs11160059	5q31	*SLC22A4*	SBP $2x10^{-8}$	
	rs17365948	8q23	*YWHAZ*	SBP $2x10^{-8}$	
	rs12279202	11p15	*IPO7*	SBP $5x10^{-8}$	
	rs3751664	16p13	*CACNA1H*	SBP $7x10^{-8}$	
Amish Cohort	rs6749447	2q24	*STK39*	SBP $8x10^{-5}$	Wang et al., 2009

Note: DBP — diastolic blood pressure; SBP — systolic blood pressure; HT — hypertension

common variants on current genotyping platforms due to differences in genetic ancestry (Franceschini et al., 2011).

The results from recent GWAS confirm the findings from previous linkage and candidate gene studies that show that no single genomic region has a large effect on blood pressure. It appears that common variants associated with blood pressure phenotypes have a very small effect, and that there is no such thing as an hypertension gene. It is more likely that a combination of many genes, each which contribute a small effect, is responsible for blood pressure variation.

Pharmacogenomics and Hypertension

The current pharmacological treatment of hypertension involves the use of direct or indirect vasodilators. First line treatment, after lifestyle modification, consists of ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and thiazide diuretics (Carratero, 2005). The choice of an antihypertensive agent by the physician is currently empirical, based on the presence of comorbidities or pharmacological interaction with other prescribed agents (Ma & Stafford, 2008). However, approximately 40–60% of patients will not respond to monotherapy, and will require polytherapy or a change to a different antihypertensive class. This suggests that the current method of hypertension management is suboptimal (Johnson et al., 2009).

Pharmacological management of hypertension is a complicated, multifactorial process, involving patient adherence, the correct antihypertensive agent, and the correct dosage. Genetic variation has been identified as having a large role in successful blood pressure control. Recent research into the pharmacogenomics of hypertension has aimed to identify genetic predictors of blood pressure lowering in response to the different classes of antihypertensive agents, and also to the adverse metabolic effects produced in susceptible individuals (Johnson et al., 2009).

The central dogma of pharmacogenomics is that the patient's response to pharmaceutical agents is influenced by variations in proteins encoded by the genome. Genetic approaches to the treatment of hypertension focus on pharmacodynamic processes that determine a drug's effect at or after it reaches its point of action. An example of a polymorphism that influences pharmacodynamics is that of the gene encoding the CYP2D6 enzyme. As part of the cytochrome P-450 enzyme family, CYP2D6 causes hydroxylation of debrisoquine, an adrenergic inhibitor used in the treatment of essential hypertension. In the 1980s, it

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was discovered that individuals who were poor metabolizers of debrisoquine were also poor metabolizers of other medications that were processed by the same enzyme family. Classical pharmacogenetics was based on discoveries like this, that single genes can determine drug metabolism (Mahgoub et al., 1977; Gonzalez et al., 1988; Weber, 1997). However, genotyping at this locus has not achieved widespread clinical use.

Within the renin-angiotensin-aldosterone system, one SNP in the angiotensinogen (*AGT*) gene has been found to be an important predictor of patient response to ACE inhibitor therapy. This SNP (rs699) results in a methionine to threonine amino acid substitution in the angiotensinogen protein due to a T to C substitution in exon 2, codon 268 (formerly thought to be codon 235). Subjects with the threonine amino acid tend to have higher plasma levels of angiotensinogen (Jeunemaitre et al., 1992; Bloem et al., 1995). A study by Hingorani et al., (1995) found that this SNP was strongly associated with a decrease in systolic ($P = .004$) and diastolic ($P = .009$) blood pressure after treatment for four weeks with an ACE inhibitor. The highest decrease was found in individuals with either the T/T or T/C genotype (Hingorani et al., 1995). However other investigations, such as the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA) trial, found no association between this T to C polymorphism and blood pressure response to irbesartan, an angiotensin II receptor antagonist (Kurland et al., 2001).

The influence of polymorphisms on patient responses to thiazide diuretics was reported in 2001 (Turner et al., 2001). A polymorphism at the G-protein β3 inhibitory subunit locus, C825T, resulted in a cytosine-to-thymine substitution. Turner et al., (2001) reported that, in patients suffering hypertension, a greater mean reduction in systolic pressure occurred after thiazide treatment in patients who were homozygous for the T/T allele and those heterozygous for the C/T allele when compared to those homozygous for the C/C allele.

Candidate genes for antihypertensive and adverse responses have been selected from the pathways and systems by which current antihypertensive medications lower blood pressure. This research is helping to elucidate the mechanisms of the differing responses to antihypertensive agents that have been observed in the population. As genome sequencing becomes more cost effective, treatment of hypertension may include analysis of the individual patient's genetic predictors of antihypertensive response. These modifiers would then influence treatment of essential hypertension, bringing individualized treatment to a new level.

Future Research

Medicine is moving steadily towards 'personalized pharmacological treatment'. Previously, analysis of pathways involved in monogenetic forms of hypertension has driven the development of antihypertensive pharmacological treatments. This research has given us ACE inhibitors, angiotensin II inhibitors, β-blockers and calcium channel blockers, but this well of information is now running dry. It was thought that genome-wide association studies would lead to the identification of new pathways and genes involved in hypertension, which would then begin to drive the development of new classes of antihypertensive agents. However, these new agents have so far failed to appear. It is becoming clearer that the future of hypertension-relevant pharmacology involves first-line analysis of an individual's genome. Understanding how an individual's genetic sequence can alter their response to treatment will improve the care of patients by enabling targeted drug therapy, while minimizing adverse reactions and side-effects.

Optimal treatment of essential hypertension involves early detection and prompt treatment. Using the pharmacogenomics approach to treatment, the most effective antihypertensive agent will be chosen as first-line treatment, adverse reactions will be avoided and side effects will be minimized for each patient. This will most likely improve patient adherence and therefore maximize the likelihood of achieving normotensive pressures. Improving the quality of health and the length of life for those suffering from essential hypertension is within the reach of modern science, and will lead to a reduced burden of disease not only for the individual, but for our society as a whole.

References

Acuna, R., Martinez-de-la-Maza, L., Ponce-Coria, J., Vazquez, N., Ortal-Vite, P., Pacheco-Alvarez, D., Bobadilla, N. A., & Gamba, G. (2011). Rare mutations in SLC12A1 and SLC12A3 protect against hypertension by reducing the activity of renal salt cotransporters. *Journal of Hypertension, 29*, 475–483.

Adeyemo, A., Gerry, N., Chen, G., Herbert, A., Doumatey, A., Huang, H., Zhou, J., Lashley, K., Chen, Y., Christman, M., & Rotimi, C. (2009). A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genetics, 5*, e1000564.

Asai, T., Ohkubo, T., Katsuya, T., Higaki, J., Fu, Y., Fukuda, M., Hozawa, A., Matsubara, M., Kitaoka, H., Tsuji, I., Araki, T., Satoh, H., Hisamichi, S., Imai, Y., & Ogihara, T. (2001). Endothelin-1 gene variant associates with blood pressure in obese Japanese subjects: The Ohasama Study. *Hypertension, 38*, 1321–1324.

Benetos, A., Gautier, S., Ricard, S., Topouchian, J., Asmar, R., Poirier, O., Larosa, E., Guize, L., Safar, M., Soubrier, F., & Cambien, F. (1996). Influence of angiotensin converting enzyme and angiotensin II type 1 receptor gene polymorphisms on aortic stiffness in normotensive and hypertensive patients. *Circulation, 94*, 698–703.

https://doi.org/10.1375/twin.14.4.295 Published online by Cambridge University Press

Benjafield, A. V., Katyk, K., & Morris, B. J. (2003). Association of *EDNRA*, but not *WNK4* or *FKBP1B*, polymorphisms with essential hypertension. *Clinical Genetics, 64*, 433–438.

Bloem, L. J., Manatunga, A. K., Tewksbury, D. A., & Pratt, J. H. (1995). The serum angiotensinogen concentration and variants of the angiotensinogen gene in white and black children. *Journal of Clinical Investigation, 95*, 948–953.

Bonnardeaux, A., Davies, E., Jeunemaitre, X., Fery, I., Charru, A., Clauser, E., Tiret, L., Cambien, F., Corvol, P., & Soubrier, F. (1994). Angiotensin II type 1 receptor gene polymorphism in human essential hypertension. *Hypertension, 24*, 63–69.

Cabadak, H., Orun, O., Nacar, C., Dogan, Y., Guneysel, O., Fak, A. S., & Kan, B. (2011). The Role of G Protein beta3 Subunit Polymorphisms C825T, C1429T, and G5177A in Turkish Subjects with Essential Hypertension. *Clinical and Experimental Hypertension, 33*, 202–208.

Carratero, O. A. (2005). Novel mechanism of action of ACE and its inhibitors. *American Journal of Heart and Circulatory Physiology, 289*, 1796–1797.

Cheng, X., & Xu, G. (2009). Association between aldosterone synthase *CYP11B2* polymorphism and essential hypertension in Chinese: A meta-analysis. *Kidney and Blood Pressure Research, 32*, 128–140.

Conen, D., Cheng, S., Steiner, L. L., Buring, J. E., Ridker, P. M., & Zee, R. Y. (2009). Association of 77 polymorphisms in 52 candidate genes with blood pressure progression and incident hypertension: The Women's Genome Health Study. *Journal of Hypertension, 27*, 476–483.

Cui, J., Zhou, X., Chazaro, I., DeStefano, A. L., Manolis, A. J., Baldwin, C. T., & Gavras, H. (2003). Association of polymorphisms in the promoter region of the *PNMT* gene with essential hypertension in African Americans but not in whites. *American Journal of Hypertension, 16*, 859–863.

Davis, G. K., & Roberts, D. H. (1997). Molecular genetics of the renin-angiotensin system: implications for angiotensin II receptor blockade. *Pharmacology & Therapeutics, 75*, 43–50.

Dzau, V. J., Antman, E. M., Black, H. R., Hayes, D. L., Manson, J. E., Plutzky, J., Popma, J. J., & Stevenson, W. (2006). The cardiovascular disease continuum validated: Clinical evidence of improved patient outcomes: Part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation, 114*, 2850–2870.

Ehret, G. B., Morrison, A. C., O'Connor, A. A., Grove, M. L., Baird, L., Schwander, K., Weder, A., Cooper, R. S., Rao, D. C., Hunt, S. C., Boerwinkle, E., & Chakravarti, A. (2008). Replication of the Wellcome Trust genome-wide association study of essential hypertension: The Family Blood Pressure Program. *European Journal of Human Genetics, 16*, 1507–1511.

Facemire, C. S., Nixon, A. B., Griffiths, R., Hurwitz, H., & Coffman, T. M. (2009). Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension, 54*, 652–658.

Fan, X., Wang, Y., Sun, K., Zhang, W., Yang, X., Wang, S., Zhen, Y., Wang, J., Li, W., Han, Y., Liu, T., Wang, X., Chen, J., Wu, H., & Hui, R. (2007). Polymorphisms of *ACE2* gene are associated with essential hypertension and antihypertensive effects of Captopril in women. *Clinical Pharmacology and Therapeutics, 82*, 187–196.

Franceschini, N., Reiner, A. P., & Heiss, G. (2011). Recent findings in the genetics of blood pressure and hypertension traits. *American Journal of Hypertension, 24*, 392–400.

Fu, Z., Nakayama, T., Sato, N., Izumi, Y., Kasamaki, Y., Shindo, A., Ohta, M., Soma, M., Aoi, N., Sato, M., Ozawa, Y., & Ma, Y. (2008). A haplotype of the *CYP4A11* gene associated with essential hypertension in Japanese men. *Journal of Hypertension, 26*, 453–461.

Gonzalez, F. J., Skoda, R. C., Kimura, S., Umeno, M., Zanger, U. M., Nebert, D. W., Gelboin, H. V., Hardwick, J. P., & Meyer, U. A. (1988). Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature, 331*, 442–446.

Gu, D., Ge, D., Snieder, H., He, J., Chen, S., Huang, J., Li, B., Chen, R., & Qiang, B. (2006). Association of alpha1A adrenergic receptor gene variants on chromosome 8p21 with human stage 2 hypertension. *Journal of Hypertension, 24*, 1049–1056.

Gu, D., Su, S., Ge, D., Chen, S., Huang, J., Li, B., Chen, R., & Qiang, B. (2006). Association study with 33 single-nucleotide polymorphisms in 11 candidate genes for hypertension in Chinese. *Hypertension, 47*, 1147–1154.

Hingorani, A. D., Jia, H., Stevens, P. A., Hopper, R., Dickerson, J. E., & Brown, M. J. (1995). Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. *Journal of Hypertension, 13*, 1602–1609.

Ho, J. E., Levy, D., Rose, L., Johnson, A. D., Ridker, P. M., & Chasman, D. I. (2011). Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study. *Journal of Hypertension, 29*, 62–69.

Hong, K. W., Jin, H. S., Lim, J. E., Kim, S., Go, M. J., & Oh, B. (2010). Recapitulation of two genomewide association studies on blood pressure and essential hypertension in the Korean population. *Journal of Human Genetics, 55*, 336–341

Jachymova, M., Horky, K., Bultas, J., Kozich, V., Jindra, A., Peleska, J., & Martasek, P. (2001). Association of the Glu298Asp polymorphism in the endothelial nitric oxide synthase gene with essential hypertension resistant to conventional therapy. *Biochemical and Biophysical Research Communications, 284*, 426–430.

Jeunemaitre, X., Soubrier, F., Kotelevtsev, Y. V., Lifton, R. P., Williams, C. S., Charru, A., Hunt, S. C., Hopkins, P. N., Williams, R. R., & Lalouel, J. M. (1992). Molecular basis of human hypertension: Role of angiotensinogen. *Cell, 71*, 169–180.

Jiang, Z., Zhao, W., Yu, F., & Xu, G. (2001). Association of angiotensin II type 1 receptor gene polymorphism with essential hypertension. *Chinese Medical Journal (English), 114*, 1249–1251.

Johnson, J. A., Boerwinkle, E., Zineh, I., Chapman, A. B., Bailey, K., Cooper-DeHoff, R. M., Gums, J., Curry, R. W., Gong, Y., Beitelshees, A. L., Schwartz, G., & Turner, S. T.

https://doi.org/10.1375/twin.14.4.295 Published online by Cambridge University Press

(2009). Pharmacogenomics of antihypertensive drugs: Rationale and design of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study. *American Heart Journal, 157*, 442–449.

Kamide, K., Kokubo, Y., Fukuhara, S., Hanada, H., Yang, J., Kada, A., Nagura, J., Takiuchi, S., Horio, T., Kawano, Y., Okayama, A., Tomoike, H., & Miyata, T. (2007). Protein tyrosine kinase 2β as a candidate gene for hypertension. *Pharmacogenetics and Genomics, 17*, 931–939.

Kamide, K., Kokubo, Y., Yang, J., Matayoshi, T., Inamoto, N., Takiuchi, S., Horio, T., Miwa, Y., Yoshii, M., Tomoike, H., Tanaka, C., Banno, M., Okuda, T., Kawano, Y., & Miyata, T. (2007). Association of genetic polymorphisms of *ACADSB* and *COMT* with human hypertension. *Journal of Hypertension, 25*, 103–110.

Keavney, B., Mayosi, B., Gaukrodger, N., Imrie, H., Baker, M., Fraser, R., Ingram, M., Watkins, H., Farrall, M., Davies, E., & Connell, J. (2005). Genetic variation at the locus encompassing 11-beta hydroxylase and aldosterone synthase accounts for heritability in cortisol precursor (11-deoxycortisol) urinary metabolite excretion. *Journal of Clinical Endocrinology and Metabolism, 90*, 1072–1077.

Kosuge, K., Soma, M., Nakayama, T., Aoi, N., Sato, M., Izumi, Y., & Matsumoto, K. (2007). A novel variable number of tandem repeat of the natriuretic peptide precursor B gene's 5'-flanking region is associated with essential hypertension among Japanese females. *International Journal of Medical Sciences, 4*, 146–152.

Kurland, L., Melhus, H., Karlsson, J., Kahan, T., Malmqvist, K., Ohman, K. P., Nystrom, F., Hagg, A., Lind, L., & Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol, T. (2001). Angiotensin converting enzyme gene polymorphism predicts blood pressure response to angiotensin II receptor type 1 antagonist treatment in hypertensive patients. *Journal of Hypertension, 19*, 1783–1787.

Levy, D., Ehret, G., Rice, K., Verwoert, G. C., Launer, L. J., Dehghan, A., Glazer, N. L., Morrison, A. C., Johnson, A. D., Aspelund, T., Aulchenko, Y., Lumley, T., Köttgen, A., Vasan, R. S., Rivadeneira, F., Eiriksdottir, G., Guo, X., Arking, D. E., Mitchell, G. F., Mattace-Raso, F. U., Smith, A. V., Taylor, K., Scharpf, R. B., Hwang, S. J., Bis, J., Harris, T. B., Ganesh, S. K., O'Donnell, C. J., Hofman, A., Rotter, J. I., Coresh, J., Benjamin, E. J., Uitterlinden, A. G., Heiss, G., Fox, C. S., Witteman, J. C., Boerwinkle, E., Wang, T. J., Gudnason, V., Larson, M. G., Chakravarti, A., Psaty, B. M., & van Duijn, C. M. (2009). Genome-wide association study of blood pressure and hypertension. *Nature Genetics, 41*, 677–687.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R., & Prospective Studies, C. (2002). Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. [Erratum appears in Lancet. 2003 Mar 22;361(9362):1060]. *Lancet, 360*, 1903–1913.

Lin, R., Fu, W., Zhou, W., Wang, Y., Wang, X., Huang, W., & Jin, L. (2011). Association of heme oxygenase-1 gene polymorphisms with essential hypertension and blood pressure in the Chinese Han population. *Genetic Testing and Molecular Biomarkers, 15*, 23–28.

Lou, Y., Liu, J., Li, Y., Liu, Y., Wang, Z., Liu, K., Wu, H., Niu, Q., Gu, W., Guo, Y., Li, Z., & Wen, S. (2011). Association Study of the beta2-Adrenergic Receptor Gene Polymorphisms and Hypertension in the Northern Han Chinese. *PLoS One, 6*, e18590.

Ma, J., & Stafford, R. S. (2008). Screening, treatment, and control of hypertension in US private physician offices, 2003–2004. *Hypertension, 51*, 1275–1281.

Mahgoub, A., Idle, J. R., Dring, L. G., Lancaster, R., & Smith, R. L. (1977). Polymorphic hydroxylation of Debrisoquine in man. *Lancet, 2*, 584–586.

Mashimo, Y., Suzuki, Y., Hatori, K., Tabara, Y., Miki, T., Tokunaga, K., Katsuya, T., Ogihara, T., Yamada, M., Takahashi, N., Makita, Y., Nakayama, T., Soma, M., Hirawa, N., Umemura, S., Ohkubo, T., Imai, Y., & Hata, A. (2008). Association of *TNFRSF4* gene polymorphisms with essential hypertension. *Journal of Hypertension, 26*, 902–913.

Newton-Cheh, C., Johnson, T., Gateva, V., Tobin, M. D., Bochud, M., Coin, L., Najjar, S. S., Zhao, J., et al. (2009). Genome-wide association study identifies eight loci associated with blood pressure. *Nature Genetics, 41*, 666–676.

O'Donnell, C. J., Lindpaintner, K., Larson, M. G., Rao, V. S., Ordovas, J. M., Schaefer, E. J., Myers, R. H., & Levy, D. (1998). Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. *Circulation, 97*, 1766–1772.

Oparil, S., & Haber, E. (1974a). The renin-angiotensin system (first of two parts). *New England Journal of Medicine, 291*, 389–401.

Oparil, S., & Haber, E. (1974b). The renin-angiotensin system (second of two parts). *New England Journal of Medicine, 291*, 446–457.

Org, E., Eyheramendy, S., Juhanson, P., Gieger, C., Lichtner, P., Klopp, N., Veldre, G., Döring, A., Viigimaa, M., Sõber, S., Tomberg, K., Eckstein, G., Kelgo, P., Rebane, T., Shaw-Hawkins, S., Howard, P., Onipinla, A., Dobson, R. J., Newhouse, S. J., Brown, M., Dominiczak, A., Connell, J., Samani, N., Farrall, M., Caulfield, M. J., Munroe, P. B., Illig, T., Wichmann, H. E., Meitinger, T., & Laan, M. (2009). Genome-wide scan identifies *CDH13* as a novel susceptibility locus contributing to blood pressure determination in two European populations. *Human Molecular Genetics, 18*, 2288–2296.

Putku, M., Kepp, K., Org, E., Sober, S., Comas, D., Viigimaa, M., Veldre, G., Juhanson, P., Hallast, P., Tonisson, N., Shaw-Hawkins, S., Caulfield, M. J., Khusnutdinova, E., Kozich, V., Munroe, P. B., & Laan, M. (2011). Novel polymorphic AluYb8 insertion in the *WNK1* gene is associated with blood pressure variation in Europeans. *Human Mutation* (in press).

Quintana, L. F., Guzman, B., Collado, S., Claria, J., & Poch, E. (2006). A coding polymorphism in the 12-lipoxygenase gene is associated to essential hypertension and urinary 12(S)-HETE. *Kidney International, 69*, 526–530.

https://doi.org/10.1375/twin.14.4.295 Published online by Cambridge University Press

Reckelhoff, J. F. (2000). Gender Differences in the Regulation of Blood Pressure. *Hypertension, 37*, 1199–1208.

Riddle, E. L., Rana, B. K., Murthy, K. K., Rao, F., Eskin, E., O'Connor, D. T., & Insel, P. A. (2006). Polymorphisms and haplotypes of the regulator of G protein signaling-2 gene in normotensives and hypertensives. *Hypertension, 47*, 415–420.

Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., & Soubrier, F. (1990). An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variation of serum enzyme levels. *Journal of Clinical Investigation, 86*, 1343–1346.

Rodriguez-Perez, J. C., Rodriguez-Esparragon, F., Hernandez-Perera, O., Anabitarte, A., Losada, A., Medina, A., Hernandez, E., Fiuza, D., Avalos, O., Yunis, C., & Ferrario, C. M. (2001). Association of angiotensinogen M235T and A(-6)G gene polymorphisms with coronary heart disease with independence of essential hypertension: The PROCAGENE study. Prospective Cardiac Gene. *Journal of the American College of Cardiology, 37*, 1536–1542.

Schmidt, S., van Hooft, I. M., Grobbee, D. E., Ganten, D., & Ritz, E. (1993). Polymorphism of the angiotensin I converting enzyme gene is apparently not related to high blood pressure: Dutch Hypertension and Offspring Study. *Journal of Hypertension, 11*, 345–348.

Shimodaira, M., Nakayama, T., Sato, N., Aoi, N., Sato, M., Izumi, Y., Soma, M., & Matsumoto, K. (2010). Association of *HSD3B1* and *HSD3B2* gene polymorphisms with essential hypertension, aldosterone level, and left ventricular structure. *European Journal of Endocrinology, 163*, 671–680.

Shimodaira, M., Nakayama, T., Sato, N., Naganuma, T., Yamaguchi, M., Aoi, N., Sato, M., Izumi, Y., Soma, M., & Matsumoto, K. (2010). Association study of the elastin microfibril interfacer 1 (*EMILIN1*) gene in essential hypertension. *American Journal of Hypertension, 23*, 547–555.

Shimodaira, M., Nakayama, T., Sato, N., Saito, K., Morita, A., Sato, I., Takahashi, T., Soma, M., & Izumi, Y. (2008). Association study of aromatase gene (*CYP19A1*) in essential hypertension. *International Journal of Medical Sciences, 5*, 29–35.

Sober, S., Org, E., Kepp, K., Juhanson, P., Eyheramendy, S., Gieger, C., Lichtner, P., Klopp, N., Veldre, G., Viigimaa, M., Doring, A., Putku, M., Kelgo, P., Shaw-Hawkins, S., Howard, P., Onipinla, A., Dobson, R. J., Newhouse, S. J., Brown, M., Dominiczak, A., Connell, J., Samani, N., Farrall, M., Caulfield, M. J., Munroe, P. B., Illig, T., Wichmann, H. E., Meitinger, T., & Laan, M. (2009). Targeting 160 candidate genes for blood pressure regulation with a genome-wide genotyping array. *PLoS One, 4*, e6034.

Song, S. B., Jin, H. S., Hong, K. W., Lim, J. E., Moon, J. Y., Jeong, K. H., Ihm, C. G., Lee, T. W., Oh, B., & Lee, S. H. (2011). Association between renin-angiotensin-aldosterone system-related genes and blood pressure in a Korean population. *Blood Pressure*, February 23, [Epub ahead of print].

Sun, B., Williams, J. S., Pojoga, L., Chamarthi, B., Lasky-Su, J., Raby, B. A., Hopkins, P. N., Jeunemaitre, X., Brown, N. J., Ferri, C., & Williams, G. H. (2011). Renin gene polymorphism: its relationship to hypertension, renin levels and vascular responses. *Journal of Renin Angiotensin-Aldosterone System.*

Sun, Z. J., Li, Y., Lu, J. Y., Ding, Q., Liang, Y., Shi, J. P., Li-Ling, J., & Zhao, Y. Y. (2009). Association of Ala589Ser polymorphism of *WNK4* gene with essential hypertension in a high-risk Chinese population. *Journal of Physiological Sciences, 59*, 81–86.

Takeuchi, F., Isono, M., Katsuya, T., Yamamoto, K., Yokota, M., Sugiyama, T., Nabika, T., Fujioka, A., Ohnaka, K., Asano, H., Yamori, Y., Yamaguchi, S., Kobayashi, S., Takayanagi, R., Ogihara, T., & Kato, N. (2010). Blood pressure and hypertension are associated with 7 loci in the Japanese population. *Circulation, 121*, 2302–2309.

Tamaki, S., Nakamura, Y., Tsujita, Y., Nozaki, A., Amamoto, K., Kadowaki, T., Kita, Y., Okamura, T., Iwai, N., Kinoshita, M., & Ueshima, H. (2002). Polymorphism of the angiotensin converting enzyme gene and blood pressure in a Japanese general population (the Shigaraki Study). *Hypertension Research, 25*, 843–848.

Timasheva, Y. R., Nasibullin, T. R., Zakirova, A. N., & Mustafina, O. E. (2008). Association of interleukin-6, interleukin-12, and interleukin-10 gene polymorphisms with essential hypertension in Tatars from Russia. *Biochemical Genetics, 46*, 64–74.

Tobin, M. D., Tomaszewski, M., Braund, P. S., Hajat, C., Raleigh, S. M., Palmer, T. M., Caulfield, M., Burton, P. R., & Samani, N. J. (2008). Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population. *Hypertension, 51*, 1658–1664.

Turner, S. T., Schwartz, G. L., Chapman, A. B., & Boerwinkle, E. (2001). C825T polymorphism of the G protein beta(3)-subunit and antihypertensive response to a thiazide diuretic. *Hypertension, 37*, 739–743.

Ueno, T., Soma, M., Tabara, Y., Tokunaga, K., Tahira, K., Fukuda, N., Matsumoto, K., Nakayama, T., Katsuya, T., Ogihara, T., Makita, Y., Hata, A., Yamada, M., Takahashi, N., Hirawa, N., Umemura, S., & Miki, T. (2008). Association between fatty acid binding protein 3 gene variants and essential hypertension in humans. *American Journal of Hypertension, 21*, 691–695.

Ueno, T., Tabara, Y., Fukuda, N., Tahira, K., Matsumoto, T., Kosuge, K., Haketa, A., Matsumoto, K., Sato, Y., Nakayama, T., Katsuya, T., Ogihara, T., Makita, Y., Hata, A., Yamada, M., Takahashi, N., Hirawa, N., Umemura, S., Miki, T., & Soma, M. (2009). Association of *SLC6A9* gene variants with human essential hypertension. *Journal of Atherosclerosis and Thrombosis, 16*, 201–206.

Vassilikioti, S., Doumas, M., Douma, S., Petidis, K., Karagiannis, A., Balaska, K., Vyzantiadis, A., & Zamboulis, C. (1996). Angiotensin converting enzyme gene polymorphism is not related to essential hypertension in a Greek population. *Journal of Hypertension, 9*, 700–702.

https://doi.org/10.1375/twin.14.4.295 Published online by Cambridge University Press

Wang, J. G., Staessen, J. A., Barlassina, C., Fagard, R., Kuznetsova, T., Struijker-Boudier, H. A., Zagato, L., Citterio, L., Messaggio, E., & Bianchi, G. (2002). Association between hypertension and variation in the alpha- and beta-adducin genes in a white population. *Kidney International, 62*, 2152–2159.

Wang, Y., O'Connell, J. R., McArdle, P. F., Wade, J. B., Dorff, S. E., Shah, S. J., Shi, X., Pan, L., Rampersaud, E., Shen, H., Kim, J. D., Subramanya, A. R., Steinle, N. I., Parsa, A., Ober, C. C., Welling, P. A., Chakravarti, A., Weder, A. B., Cooper, R. S., Mitchell, B. D., Shuldiner, A. R., & Chang, Y. P. (2009). From the cover: Whole-genome association study identifies *STK39* as a hypertension susceptibility gene. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 226–221.

Weber, W. (1997). Human drug-metabolizing enzyme variants. In M. Borrow, P. Harper, A. Motulsky & C. Scriver (Eds.), *Pharmacogenetics* (1st ed., pp. 131–216). New York: Oxford University Press.

Whitworth, J. A. (2003). Emerging drugs in the management of hypertension. *Expert Opinion on Emerging Drugs, 8*, 377–388.

Williams, S. S. (2007). Advances in genetic hypertension. *Current Opinion in Pediatrics, 19*, 192–198.

Wilson, F., Disse-Nicodeme, S., Choate, K., Ishikawa, K., Nelson-Williams, C., Desitter, I., Gunel, M., Milford, D., Lipkin, G., Achard, J., Feely, M., Dussol, B., Berland, Y., Unwin, R., Mayan, H., Simon, D., Farfel, Z., Jeunemaitre, X., & Lifton, R. (2001). Human hypertension caused by mutations in wnk kinases. *Science, 293*, 1107–1112.

Wong, T. Y., & Mitchell, P. (2007). The eye in hypertension [Research Support, N.I.H., Extramural Research Support, Non-U.S. Government Review]. *Lancet, 369*, 425–435.

World Health Organization, (2011). *Cardiovascular disease.* Retrieved from http://www.who.int/mediacentre/factsheets/fs317/en/index.html

Welcome Trust Case Control Consortium (WTCCC). (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature 447*, 661–678.

Wu, S. N., Zhang, Y., Gardner, C. O., Chen, Q., Li, Y., Wang, G. L., Gao, P. J., & Zhu, D. L. (2007). Evidence for association of polymorphisms in CYP2J2 and susceptibility to essential hypertension. *Annals of Human Genetics, 71*, 519–525.

Yan-Yan, L. (2011). Transforming growth factor beta1 +869T/C gene polymorphism and essential hypertension: A meta-analysis involving 2708 participants in the Chinese population. *Internal Medicine, 50*, 1089–1092.

Yang, H. C., Liang, Y. J., Wu, Y. L., Chung, C. M., Chiang, K. M., Ho, H. Y., Ting, C. T., Lin, T. H., Sheu, S. H., Tsai, W. C., Chen, J. H., Leu, H. B., Yin, W. H., Chiu, T. Y., Chen, C. I., Fann, C. S., Wu, J. Y., Lin, T. N., Lin, S. J., Chen, Y. T., Chen, J. W., & Pan, W. H. (2009). Genome-wide association study of young-onset hypertension in the Han Chinese population of Taiwan. *PLoS One, 4*, e5459.

Yi, L., Gu, Y. H., Wang, X. L., An, L. Z., Xie, X. D., Shao, W., Ma, L. Y., Fang, J. R., An, Y. D., Wang, F., & Zhang, D. L. (2006). Association of *ACE, ACE2* and *UTS2* polymorphisms with essential hypertension in Han and Dongxiang populations from north-western China. *The Journal of International Medical Research, 34*, 272–283.

Zee, R. Y., Lou, Y. K., Griffiths, L. R., & Morris, B. J. (1992). Association of a polymorphism of the angiotensin I-converting enzyme gene with essential hypertension. *Biochemical and Biophysical Research Communications, 184*, 9–15.

Zhao, Q., Fan, Z., He, J., Chen, S., Li, H., Zhang, P., Wang, L., Hu, D., Huang, J., Qiang, B., & Gu, D. (2007). Renalase gene is a novel susceptibility gene for essential hypertension: A two-stage association study in northern Han Chinese population. *Journal of Molecular Medicine, 85*, 877–885.

Zhao, W., Wang, Y., Wang, L., Lu, X., Yang, W., Huang, J., Chen, S., & Gu, D. (2009). Gender-specific association between the kininogen 1 gene variants and essential hypertension in Chinese Han population. *Journal of Hypertension, 27*, 484–490.

Zhou, X. F., Cui, J., DeStefano, A. L., Chazaro, I., Farrer, L. A., Manolis, A. J., Gavras, H., & Baldwin, C. T. (2005). Polymorphisms in the promoter region of catalase gene and essential hypertension. *Disease Markers, 21*, 3–7.

https://doi.org/10.1375/twin.14.4.295 Published online by Cambridge University Press