



A Hypertension Gene: Are We There Yet?

Samantha J. Lupton, Christine L. Chiu, and Joanne M. Lind

Unit of Molecular Physiology, School of Medicine, University of Western Sydney, Australia

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).

RECEIVED 10 May, 2011; ACCEPTED 20 May, 2011.

ADDRESS FOR CORRESPONDENCE: Joanne M. Lind, School of Medicine, University of Western Sydney, Locked Bag 1797, Penrith NSW 2751, Australia. E-mail: j.lind@uws.edu.au

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

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 β 3 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 interfacier 1 | EMILIN1 | Shimodaira et al., 2010 |
| Adrenergic | Protein tyrosine kinase 2 β | PTK2B | Kamide,et al., 2007 |
| | β 2-adrenergic receptor | ADRB2 | Lou et al., 2011 |
| | α 1A-adrenergic receptor | ADRA1A | Gu, Ge, et al., 2006 |
| | α 2A-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 |
| Other | Acyl-CoA dehydrogenase | ACADSB | Kamide et al., 2007 |
| | 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 | |

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

TABLE 2
Top Results for GWAS in Blood Pressure and Hypertension

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

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 β_3 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.

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