

Genetics of hypertension

Paul N. Hopkins, MD, MSPH and Steven C. Hunt, PhD

Hypertension is the most prevalent cardiovascular disorder. In the 1999 to 2000 NHANES survey, the prevalence of hypertension progressively increased from 7.2% in those aged 18 to 39 to 30.1% in 40 to 59 year olds and 65.4% in those 60 and older.¹ Risk of both coronary atherosclerosis and stroke increase exponentially as blood pressure rises (see Fig. 1).² Although the relative risk for stroke increases more rapidly than coronary disease, at any pressure, the absolute risk for coronary disease is considerably greater than for stroke. An insight into this finding comes from autopsy studies that show that the carotid and intracerebral vascular beds are relatively protected from atherosclerosis as compared to the coronary circulation, particularly at lower blood pressures (see Fig. 2).^{3,4} Probably the major means whereby hypertension accelerates atherosclerosis is through pressure-driven convection of LDL and other atherogenic particles into the arterial intima.^{5–8} Indeed, without at least arterial pressures, atherosclerosis does not exist in the vascular tree⁹ even in patients with homozygous familial hypercholesterolemia.^{10,11} Increased turbulence (a rare occurrence in the human circulatory system) does not increase atherosclerosis. Rather, higher sheer stress is a strong stimulus for release of nitric oxide that locally decreases risk of atherosclerosis. Focal areas of low sheer stress are at inherently increased risk of atherosclerotic disease (such as the coronary arteries where flow stops during each systole).¹²

Interestingly, in most studies, stroke risk has been affected little by serum total cholesterol,^{13,14} although some recent studies identify clear associated risk.¹⁵ At least some association with all standard cardiovascular risk factors should be expected, not only because thromboembolic stroke may be caused by carotid tree atherosclerosis, but because aortic plaques have been strongly implicated as an embolic source for ischemic stroke.^{16–18}

Hypertension is not just a risk factor for atherosclerosis. High blood pressure can have direct adverse effects on arteries, arterioles, and the heart, resulting in potentially severe consequences beyond the more common manifestations of myocardial infarction and atherothrombotic stroke. Even modestly elevated blood pressure is a major risk factor for congestive heart failure.^{19,20} Hypertension is a major contributor to left ventricular hypertrophy, a major risk factor for sudden death independent of other risk factors.^{21,22} Hypertension can lead

progressively to arterial and arteriolar hypertrophy, arteriosclerosis and arteriolosclerosis, and with very high pressures to fibrinoid change and fibrinoid necrosis in arterioles. These latter changes can result in lumen compromise of arterioles resulting in lacunar stroke, Charcot-Bouchard aneurysms, glomerulosclerosis and nephrosclerosis, and ultimately malignant hypertension in the kidney and retinal ischemia and blindness. Risk of intracerebral hemorrhage is increased 33-fold at stage 3 or higher pressures compared to normal blood pressure.²³ Untreated, malignant hypertension is associated with a 5-year mortality rate of 95% with 65% dying from congestive heart failure, 14% from renal failure, 11% from myocardial infarction, and just 5% from cerebral hemorrhage.²⁴

FAMILY HISTORY OF HYPERTENSION AND HERITABILITY OF BLOOD PRESSURE

Like premature CAD, hypertension is a familial disease. This was recognized as early as 1923 in Germany.²⁵ Using historical family data from over 94,000 individuals, we found that the risk of developing hypertension after 1970 in persons under age 50 was approximately doubled for each first degree relative that had developed hypertension before 1970.²⁶ More formal estimates of heritability of blood pressure (the percent of population variance attributable to genetic factors) frequently range between 50% and 70% for systolic and diastolic blood pressure in twin studies with considerably lower estimates (around 20%–25%) from family studies.^{27–29} Complex segregation analysis continues to show evidence for hypertension-related "major" genes.^{30,31}

HERITABILITY OF END-ORGAN DAMAGE

In addition to heritability of blood pressure, predisposition to end organ damage generally attributable to hypertension may be inherited separately from blood pressure. There are "stroke-prone" and "stroke-resistant" spontaneously hypertensive rats (SHR). Cross-breeding the two strains demonstrated independent segregation of the stroke-prone trait.³² Based on this work in SHR, which found linkage of the stroke trait to an area that included atrial natriuretic peptide, these investigators identified a variant in the atrial natriuretic peptide gene associated with a 2-fold increased risk of stroke in the large, prospective, Physician's Health Study.³³ There are relatively rare Mendelian forms of stroke, both hemorrhagic³⁴ and lacunar (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy or CADASIL)³⁵ that are unrelated to hypertension. CADASIL has a prevalence of at least 1 per 100,000 and accounts for about 2% of lacunar

From Cardiovascular Genetics, University of Utah, Salt Lake City, Utah.

Paul N. Hopkins, MD, MSPH, Professor of Internal Medicine, University of Utah, Cardiovascular Genetics, 410 Chipeta Way, Room 167, Salt Lake City, UT 84108.

Received: August 13, 2003.

Accepted: August 29, 2003.

DOI: 10.1097/01.GIM.0000096375.88710.A6

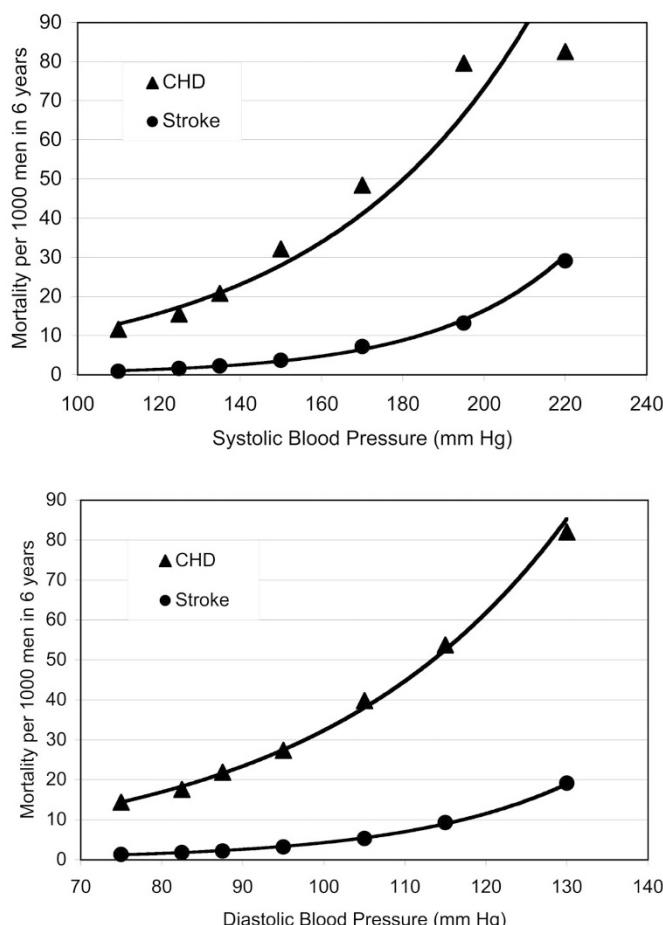


Fig. 1 Coronary heart disease (CHD) and stroke mortality in relation to systolic and diastolic blood pressure in the MRFIT study. Adapted from Neaton et al.²

strokes under age 65.³⁶ Leukoaraiosis is a diffuse lesion of white matter resulting in hyperintensity on MRI scans often seen together with lacunae and thought to be due to a form of arteriolosclerosis or “microatheroma.”³⁷ The extent of leukoaraiosis was found to be 71% heritable in World War II veteran twins.³⁸

Family history appears to influence more common types of end-organ damage, even after adjustment for blood pressure. Thus, family history of atherothrombotic stroke was associated with relative risks of 1.5 to 3 for this most common form of stroke.^{39–41} Strong evidence (LOD score 4.40) has been presented for linkage of common forms of stroke to chromosome 5q12 in Icelandic families, apparently independent of known risk factors.⁴² Family history of intracerebral hemorrhage was associated with 6-fold increased risk of having an intracerebral hemorrhage independent of blood pressure.⁴³ For subarachnoid hemorrhage, risk was increased 4-fold by a definite positive family history.⁴⁴ Left ventricular mass⁴⁵ and other measures of left ventricular size and function are heritable.⁴⁶ Pulse pressure, a measure of arterial stiffness or distensibility, was strongly heritable and related to telomere length (which was also highly heritable).⁴⁷ Carotid intima-medial thickness (IMT) has been reported to be up to 30% to 64% heritable.^{48–51}

Presence of carotid plaque was 23% heritable after correction for hypertension.⁵² One candidate gene variant (IL6-174G>C CC found in 19% of the population) was associated with much higher plasma interleukin (IL)-6 and increased carotid IMT at high alcohol intakes.⁵³ A substantial number of gene variants have been associated with carotid IMT; some were also associated with CHD.⁵⁴ These will not be discussed further in this review.

GENE-ENVIRONMENT INTERACTION

Complex modeling of blood pressure in families suggests inheritance of a gene or genes that lead to a steeper rise in blood pressure with age.^{55,56} There are multiple examples of rat or mouse strains that develop high blood pressure only when exposed to a high salt diet, most notable being the Dahl salt-sensitive rat. Chimpanzees living in a natural setting exhibit salt sensitivity in some but not all the individuals.⁵⁷

In humans, environmental stressors include moderate to high salt intake and lack of physical exertion together with an excessively rich diet resulting in a high prevalence of overweight.^{58–60} In contrast, when salt intake is very low (below 50 mEq/day), hypertension is rare.^{58,61} More recent observations document that even with a relatively high salt intake, blood pressure remains low and hypertension is rare in a rural setting with continued exercise and lean body habitus.⁶² Low maternal protein intake and genetic susceptibility can lead to reduced nephron number in several models.^{63–67} Recent identification of a substantial reduction in the number of nephrons in kidneys of relatively young primary hypertensive patients who died from accidents provide indirect evidence that such early changes in the structure of kidneys that may favor salt retention may be relevant in human primary hypertension.⁶⁸

PATHOGENESIS OF HYPERTENSION: IMPLICATIONS FOR GENETICS

The study of hypertension is complicated by the complexity of compensatory mechanisms and the difficulty in determining the initiating cause. For example, maneuvers that initially cause volume overload and hypertension in the dog eventually lead, through autoregulation of tissue blood flow, to a state of increased peripheral resistance and near normal fluid volume.⁶⁹ Indeed, the brilliant work by Guyton and coworkers, identifying the kidney as the dominant, long-term regulator of blood pressure,^{70–73} illustrates the need for an appreciation of pathophysiology when considering genetic factors potentially contributing to hypertension. Investigators continue to point out the inadequacies of simplistic Mendelian models in statistical genetics as applied to common disease and the need to consider pathophysiology, biochemistry, and molecular mechanisms in the effort to understand the effects of genetic variants in blood pressure regulation.^{74,75}

Recent identification of the genetic basis of most rare, monogenic forms of hypertension and hypotension reiterates the central role of the kidney in long-term control of blood pres-

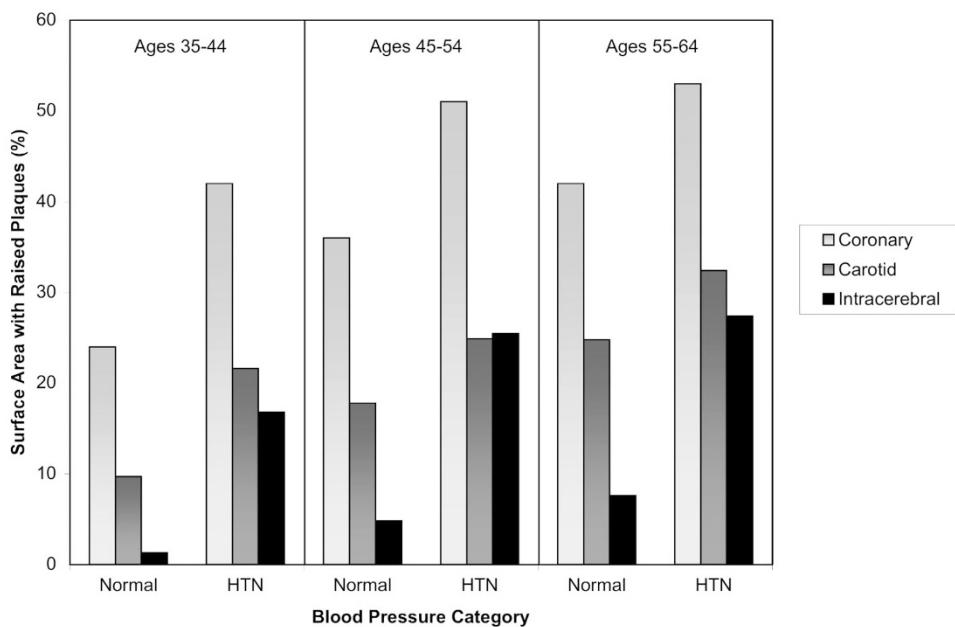


Fig. 2 Percent of surface identified with raised atherosclerotic plaques at autopsy among men from Oslo with and without diagnosed hypertension in the International Atherosclerosis Project. Adapted from Robertson et al.³ and Solberg et al.⁴

sure (Tables 1 and 2).⁷⁶ Several interesting, unsuspected new drug targets have emerged as a result of these studies. These include the chloride channel in the basolateral membrane of epithelial cells of the thick ascending loop of Henle and, possibly, more effective drugs to inhibit the epithelial sodium channel (amiloride is of limited value because it competes with sodium and is hence of little value when it is most needed—during a high salt diet). Importantly, all the monogenic hypertension syndromes identified to date are caused by defects resulting in renal salt retention, whereas all the low blood pressure syndromes share a common mechanism of excess renal sodium loss. The absence of syndromes relating to the many short-term blood pressure control systems (baroreceptors, α - or β -receptors, etc.) again emphasizes the dominant role of the kidney and its pressure-natriuresis function in long-term blood pressure control.

METABOLIC SYNDROME AND DYSLIPIDEMIC HYPERTENSION

The frequent coexistence of abnormal plasma lipids and hypertension first became strikingly apparent to us when we recruited sibling pairs for a study on hypertension (with the only criteria being onset of hypertension by age 60 in both siblings). We found triglyceride and HDL abnormalities 3 times more frequent in this group than expected for a general population.^{77,78} We coined the term familial dyslipidemic hypertension as a descriptive, clinical diagnosis. Subsequent studies in twins confirmed a genetic predisposition to the coexistence of both hypertension and dyslipidemia and emphasized the markedly greater risk for CAD when both hypertension and dyslipidemia were present as compared to either separately.⁷⁹ Using data from this study, 46% of CAD risk

associated with hypertension can be attributed to the frequently accompanying lipid abnormalities. This may help explain why blood pressure reduction with antihypertensives alone achieves only about half the expected reduction in CAD.⁸⁰ Much greater reductions in CAD risk were achieved in a Swedish primary prevention trial when both blood pressure and lipids were reduced.⁸¹ Further insight into the syndrome comes from the recognition that fully 80% of all incident hypertension (with a strong increasing gradient in risk) was attributable to subscapular skinfold above 9 mm in the Framingham Offspring study.⁵⁹

Genetic epidemiology strongly points to an interaction between excess accumulation of fat, particularly when centrally distributed, and genetic predisposition that leads to the major features of the metabolic syndrome: hypertension, diabetes, and dyslipidemia.^{78,82–85} Overweight may only be associated with increased coronary risk when accompanied by hypertension.⁸⁶ Fig. 3 illustrates how virtually all features of the metabolic syndrome can be related to excess fat accumulation (particularly in visceral and in muscle tissues but other tissues as well). Tissue-specific insulin resistance can be induced by selected tissue expression of lipoprotein lipase and uptake of excess fat.⁸⁷ Excess fat accumulation can have toxic cellular effects in many tissues including heart and β cells of the pancreas.^{88,89}

Genetic insights regarding dyslipidemic hypertension are beginning to emerge. A locus for blood pressure, fasting insulin, and leptin was found on chromosome 7q.⁹⁰ A locus on chromosome 1q21-q23 (near 170 to 180 cM) has been linked in various genome scans to familial combined hyperlipidemia,^{91–93} diabetes,⁹⁴ and blood pressure.^{95–97} A similar locus on chromosome 4p may exist.⁹⁸ The Lys198Asn variant in the endothelin-1 gene (on 6p24-p23) appears to interact with BMI

Table 1.
Monogenic syndromes resulting in early onset, severe hypertension

Syndrome, transmission, defect, (abbreviation, gene location)	Pathophysiology, comments
Glucocorticoid remedial hyperaldosteronism Autosomal dominant	Aldosterone synthase activity ectopically expressed in adrenal zona fasciculata due to chimeric promoter region of 11 β -hydroxylase (under control of ACTH). Results in elevated aldosterone despite low plasma renin, increased epithelial sodium channel (ENaC) expression and Na ⁺ resorption in connecting tubule and collecting duct. Excess aldosterone secretion suppressed by glucocorticoid administration (suppresses ACTH). Hypokalemia, metabolic alkalosis (due to increase secretion of K ⁺ and H ⁺) are variably expressed. HTN responsive to spironolactone, suppressed by prednisone.
Unequal fusion (chimera) of two, similar and adjacent genes, aldosterone synthase (<i>CYP11B2</i>) and 11 β -hydroxylase (<i>CYP11B1</i>) due to an unequal crossing-over event (8p21)	
Apparent mineralocorticoid excess Autosomal recessive	Cortisol, which activates the mineralocorticoid receptor (MR) as well as aldosterone, is not converted normally to cortisone (no MR activity). Low renin, absence of circulating aldosterone, hypokalemia, and metabolic alkalosis. A mouse model also shows hypertension.
Deficiency of 11 β -hydroxysteroid dehydrogenase-2 (<i>HSD11B2</i> , <i>AME1</i> , 16q22)	
Steroid 11 β -hydroxylase deficiency (Congenital adrenal hyperplasia IV) Autosomal recessive (<i>CYP11B1</i> , 8q21)	11 β -Hydroxylase is required for cortisol synthesis. Deficiency results in increased ACTH and increased production of both deoxycorticosterone and corticosterone which can activate the MR. Aldosterone is suppressed, hypokalemic alkalosis present.
Steroid 17 α -hydroxylase deficiency (Congenital adrenal hyperplasia V) Autosomal recessive (<i>CYP17</i> , 10q24.3)	Similar to steroid 11 β -hydroxylase deficiency.
Hypertension with severe exacerbated in pregnancy Autosomal dominant MR Ser810Leu (<i>NR3C2</i> , MR, 4q31.1)	Carriers have hypertension onset before age 20 with severe worsening in pregnancy. Low renin phenotype. 801Leu variant results in modification of the MR causing promiscuous activation by a variety of compounds (e.g., progesterone and spironolactone) that normally bind without activating MR. Normally MR has specificity for 21-hydroxylated steroids.
Liddle syndrome Autosomal dominant	Defect or loss of PPPXY sequence in the cytoplasmic C terminus of either the β or γ subunits of ENaC results in loss of affinity for clathrin (and loss of normal removal into clathrin-coated pits) and reduced clearance of ENaC from the luminal brush border. Nedd4-1 and Nedd4-2, proteins that recognize the PPPXY domain and ubiquitinate ENaC, marking it for degradation, may also be involved.
Deletions of cytoplasmic tail and some missense mutations of the epithelial sodium channel (ENaC) (<i>SCNN1B</i> , 16p13-p12)	
Pseudohypoaldosteronism, type II (Gordon's syndrome) (<i>WNK1</i> , 12p13) (<i>WNK4</i> , 17q21-q22) (Also linkage to 1q31-q42)	The clinical features of Gordon's syndrome include hypertension, hyperkalemia, hyperchloraemia, metabolic acidosis, salt (and chloride) sensitivity, and responsiveness to low-dose thiazide diuretics. WNK1 mutations causing Gordon's syndrome are gain-in-function mutations. WNK1 appears to increase activity of the thiazide-sensitive Na-Cl cotransporter (NCCT) causing increased Na-Cl transport. WNK4 normally suppresses NCCT with the mutant form leading to impaired WNK4 activity and increased NCCT activity.
Hypertension with brachydactyly mapped to 12p12.2-11.2	Not salt sensitive or associated with abnormalities of the renin-angiotensin system. Unknown mechanism.
Bardet-Biedl syndrome (<i>BBS2</i> , 16q21) (<i>BBS4</i> , 15q22.3-q23)	Mechanism of disease unknown.
Autosomal dominant polycystic kidney disease (<i>PKD1</i> , 16p13.3) (<i>PKD2</i> , 4q21-q23)	Common (1 in 500–1000). May be considered a genetic cause of secondary hypertension (due to activation of the renin-angiotensin system secondary to compressive effects of cysts). 75% of patients have hypertension, frequently severe.

resulting in mildly greater risk for hypertension in 198Asn carriers with higher BMI.^{99–101} The 460Trp variant of α -adducin also appeared to interact with BMI and triglycerides.¹⁰² A variant of the SA gene (*SAH*) was associated with increased BMI, waist/hip ratio, triglycerides, and blood pressure.¹⁰³ The Trp64Arg variant of the β_3 -adrenergic receptor (*ADRB3*) has similarly been associated with multiple features of the metabolic syndrome.¹⁰⁴

GENOME-WIDE SCANS FOR HYPERTENSION

At least 22 genome-wide scans have been reported to identify loci for blood pressure. Methodologies differed, some using blood pressure as a quantitative phenotype, others using hypertension. Some scans utilized families, others affected or dissimilar sibling pairs. The results of these scans are reviewed in Table 3. Linked loci with at least suggestive LOD scores were

Table 2.
Monogenic syndromes of low blood pressure

Syndrome, transmission, defect, (gene abbreviation, location)	Pathophysiology, comments
Aldosterone synthase deficiency Autosomal recessive (<i>CYP11B2</i> , 8p21)	Impaired aldosterone synthesis leads to impaired distal sodium resorption, hypovolemia, hypotension, and shock. Impaired K ⁺ and H ⁺ excretion with hyperkalemia and metabolic acidosis also seen.
Congenital adrenal hyperplasia 1 steroid 21-hydroxylase deficiency Autosomal recessive (<i>CYP21A2</i> , 6p21.3)	Similar to aldosterone synthase deficiency. Other endocrine abnormalities.
Dominant Pseudohypoaldosteronism, type I Autosomal dominant	Neonatal hypotension, severe salt wasting, marked hyperkalemia and metabolic acidosis despite elevated aldosterone. Normally, ENaC, under control of aldosterone, establishes the luminal electronegative potential that allows normal K ⁺ and H ⁺ excretion. Once a typical salt-rich diet is established, the phenotype reverts to normal with no manifestations of disease in the adult.
Mineralocorticoid receptor loss of function (various mutations seen) (<i>MR</i> , 4q31.1)	
Recessive Pseudohypoaldosteronism, type I Autosomal recessive (<i>SCNN1A</i> , 12p13) (<i>SCNN1B</i> , 16p13-p12) (<i>SCNN1G</i> , 16p13-p12)	Loss of ENaC function leads to salt wasting, hypovolemia, hyperkalemia, metabolic acidosis (due to impaired K ⁺ and H ⁺ excretion) in neonatal period despite high serum aldosterone. Unlike dominant form, recessive does not correct with age.
Gitelman syndrome Autosomal recessive Sodium chloride cotransporter (<i>SLC12A3</i> , 16q13)	Impaired function of the thiazide-sensitive Na-Cl cotransporter (<i>SLC12A3</i>) of the distal convoluted tubule results in salt wasting. A compensatory increase in the renin-angiotensin-aldosterone system minimizes salt loss, but the increase in distal ENaC leads to increased K ⁺ and H ⁺ excretion. A decrease in urinary calcium is seen together with excess magnesium excretion. Heterozygotes frequently maintain normal blood pressure by increased salt intake.
Bartter syndrome Autosomal recessive (type 1— <i>SLC12A1</i> , 15q15-q21) (type 2— <i>ROMK</i> or <i>KCNJ1</i> , 11q24) (type 3— <i>CLCNKB</i> , 1q36)	Loss of function of the apical, furosemide-sensitive, Na-K-2Cl cotransporter (<i>SLC12A1</i>) in the thick ascending loop of Henle (TAL) results in marked salt wasting, activation of the renin-angiotensin-aldosterone system, hypokalemia, and metabolic alkalosis. Deficiency of ROMK (the ATP-sensitive K ⁺ channel) leads to a similar phenotype. ROMK is required in the TAL because K ⁺ is low in the TAL tubular fluid and must be excreted back into the tubular lumen in order to facilitate further NaCl reabsorption. CLCNKB is a chloride channel in the basolateral membrane of TAL epithelial cells. Na ⁺ entering via the Na-K-2Cl cotransporter exits by way of the basolateral Na ⁺ /K ⁺ ATPase. Cl ⁻ must leave by way of CLCNKB. All forms have increased urinary calcium and less magnesium wasting as compared to Gitelman syndrome.

seen on every chromosome. Perhaps most striking is the lack of consistently linked loci. This may serve to illustrate the heterogeneity of human hypertension as well as the potential shortcomings of attempting to compare studies using different methodologies. The difficulty in finding reproducible loci for hypertension has been the subject of a number of recent commentaries.^{105,106} Currently, identifying susceptibility genes and variants from genome scans remains elusive.

PROGRESS IN CANDIDATE GENES FOR COMMON, PRIMARY HYPERTENSION

Thus far, the candidate gene approach has provided more examples than the linkage approach of gene variants that appear to affect blood pressure. Reasonable candidate genes to consider include genes related to physiological systems known to be involved

in the control of blood pressure and genes known to affect blood pressure in mouse models. Effects on blood pressure of gene knockouts in mice are shown in Table 3.^{107,108} Lessons learned from the studies of candidate genes to date include the shortcomings that result from limited statistical power of many studies, expected variation from one population to another, the need for better phenotyping of study subjects, the relatively small effect of the genes studied on population prevalence of hypertension, and the lack of sufficient certainty of consequences of any genes studied thus far to make treatment recommendations based on genotype.¹⁰⁹ Keeping these limitations in mind, results of candidate gene studies will be briefly reviewed.

Angiotensinogen (AGT)

AGT was the first gene to show linkage with human essential or primary hypertension.¹¹⁰ In addition to linkage to the AGT

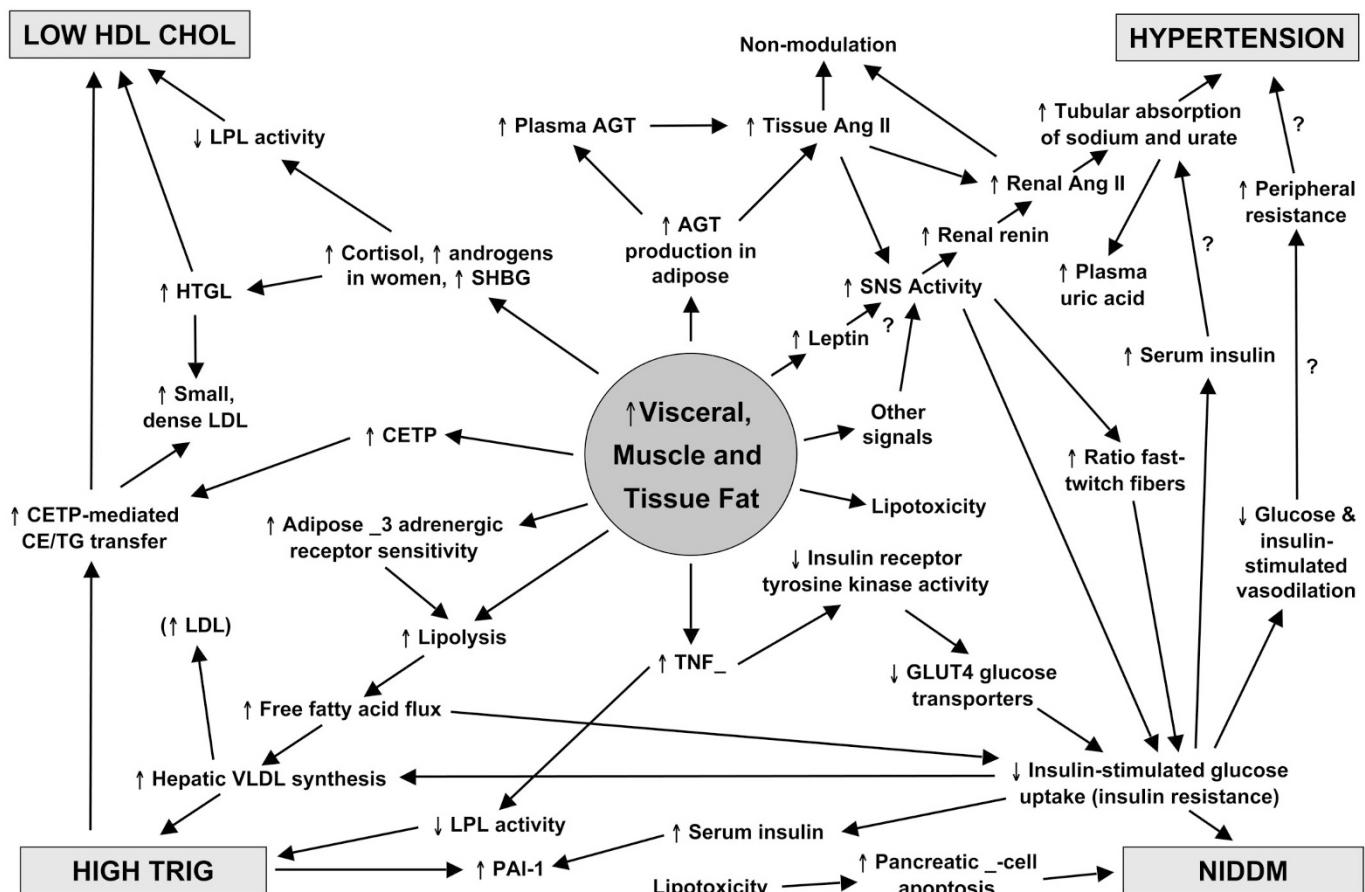


Fig. 3 Suggested pathophysiology of the metabolic syndrome.

locus, hypertension and plasma angiotensinogen levels were both found to be associated with the 235T and 174M variants of *AGT*.¹¹⁰ Numerous studies followed with mixed but mostly positive results. A metaanalysis of 69 association studies with 27,906 subjects concluded that the *AGT* 235 TT genotype conferred 31% greater risk for hypertension ($P = 0.001$), whereas those with the MT genotype had 11% greater risk ($P = 0.03$).¹¹¹ The effect was most frequently found in Caucasian populations and in males. The *AGT* 235T polymorphism, without any apparent functional significance itself, is in almost complete linkage disequilibrium with the -6A variant in the promoter region of *AGT*, which, in expression studies, was found to result in an increase in function compared to the -6G allele.¹¹² In the large Family Blood Pressure Program metaanalysis, *AGT* -6A was associated with the diagnosis of hypertension but not with higher blood pressure in the normal range.¹¹³ Subsequent studies have continued to find mixed, but generally positive association.^{114–119} Blood pressure responses to an angiotensin converting enzyme inhibitor were greater among those with the 235T allele in one study,¹²⁰ whereas another group reported negative findings.¹²¹

How might certain variants of the *AGT* gene promote essential hypertension? Detailed reviews are available.¹²² Several studies suggest a significant effect of *AGT* genotype on plasma

angiotensinogen levels, with higher levels found in variants associated with higher blood pressure.^{110,123–125} Plasma angiotensinogen levels have, in turn, been associated with blood pressure on the population level.¹²⁶ Both urinary and plasma aldosterone were found higher in those with the *AGT* -6A variant.¹²⁷ Targeted gene disruption and duplication to vary *AGT* gene number (from 1 to 4) resulted in variations in plasma angiotensinogen ranging from 35% to 145% of normal in mice. These differences in angiotensinogen levels correlated directly with blood pressure.¹²⁸

Because angiotensinogen is relatively rate limiting while the reaction involving angiotensin converting enzyme (ACE) displays more complex kinetics (as ACE activity increases, angiotensin I falls rapidly with essentially no change in angiotensin II production), excess angiotensinogen appears to lead to excess angiotensin II production, especially at the tissue level, whereas overexpression of ACE does not. Only marked inhibition of ACE results in a reduction in angiotensin II.¹²⁹ In other studies using transgenic mice, overexpressing human renin and angiotensinogen either systemically or with excess angiotensinogen production restricted to the kidney resulted in equally elevated blood pressure.¹³⁰ In this study, losartan was effective in treating the hypertension induced by overexpression of systemic angiotensinogen, but was only modestly effec-

Table 3.
Genome-wide scans reporting suggestive (LOD 1.9) or greater evidence for blood pressure-related traits

Ref.	Trait	Sample	Chromosome and location (cM) of linkage																							
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	X			
Krushkal ⁹⁵	SBP	W, S		58			190	144*											97							
Xu ²⁷¹	SBP	C, S			6	73							58						24			39				
	DBP	C, S										46				10	64				39	25				
																		5								
Levy ⁹⁶	SBP	W, F																	67*							
																			94							
	DBP	W, F																	74	7						
Rice ²⁷²	SBP	W, F		97			32		135	87											4					
				103																						
Hsueh ²⁷³	DBP	W, F		210*																						
Sharma ²⁷⁴	HTN	W, S																								
Perola ²⁷⁵	HTN	W, S		185	166*																39	67				
Zhu ²⁷⁶	HTN	C, S		161																						
Atwood ²⁷⁷	SBP	W, F																	116		37					
	DBP	MA, F		99*															165							
Atwood ²⁷⁸	PP	MA, F											114	154						116		37				
Cheng ⁹⁰	SBP	W, F	4										128													
	MAP	W, F	4																							
Hunt ⁹⁷	HTN	W, F	192										58				83		10							
													127						3							
	SBP	W, F											89*													
Allayee ⁹⁸	SBP	W, F			90*																10					
	DBP	W, F											89													
Angius ²⁷⁹	HTN	W, F	12*										43				11	79	15		54*					
																	5									
Harrap ²⁸⁰	SBP	W, S	76		117														49				42			
Rice ²⁸¹	SBP	W, F											10													
	SBP	B, F											5											49		
	DBP	B, F														95										
Cooper ²⁸²	SBP	B, F																			47	78				
	DBP	B, F	104	16									81		76											
													109													
Kristjansson ²⁸³	HTN	W, F																		89*						
Ranade ²⁸⁴	HTN	C, S											30				10					0				
Thiel ²⁸⁵	DBP	W, F	170		119																					
Rao ²⁸⁶	HTN	B, S		63																						
Kardia ²⁸⁷	HTN	W, S																								
	HTN	B, S																								
Caulfield ²⁸⁸	HTN	W, S					190*						145													

HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; W, white; B, Black; C, Chinese; MA, Mexican-American; F, families; S, siblings.

*LOD scores 3.0 +

Table 4.

Effect on systolic blood pressure of gene knockouts in adult mice

Gene inactivation	BP change (mm Hg)
Renin-angiotensin system	
Renin	-30
Angiotensinogen	-30
Angiotensin type 1 receptor	-30
Angiotensin type 2 receptor	+10
11 β -Hydroxysteroid dehydrogenase type 2	+20
Ion transporters and regulators	
Epithelial Na channel (amiloride-sensitive) (low salt)	-20
Na-Cl cotransporter (thiazide-sensitive) (low salt)	-10
Na-K-2Cl cotransporter 1 (furosemide-sensitive) (normal salt)	-20
Na-K-2Cl cotransporter 2 (furosemide-sensitive) (normal salt)	-20
Na/H exchanger 3 (normal salt - low salt lethal)	-30
Dopamine type 1A receptor	+25
Dopamine type 3 receptor	+20
Atrial natriuretic peptide	+15
Atrial natriuretic peptide type A receptor	+16
Natriuretic peptide receptor/Guanylyl cyclase-A (<i>NPR1</i>)	+34
Vasoactive and other factors	
Endothelial nitric oxide synthase	+20
Prostaglandin EP2 receptor	+10
Endothelin 1	+10
Endothelin type B receptor	+20
Glomerular epithelial protein 1	+15
Bradykinin type 2 receptor (with high salt)	+15
Neutral endopeptidase	-25
Insulin receptor substrate 1	+10
Insulin growth factor 1	+10
Calcium-dependent potassium channel β -1 subunit	+20
Adenosine type A2a receptor	+20
Dopamine- and cyclic AMP-regulated phosphoprotein	+15
Bombesin type 3 receptor	+15
Fibroblast growth factor 2	-20
Apolipoprotein E	+22
Cytochrome p450 monooxygenase 4A14 (males/females)	+30/+17
Heme oxygenase 1	+24

pressure.¹³¹ Antisense oligonucleotides to *AGT* injected into the brain of 2-kidney, 1 clip rats also reduced blood pressure substantially.¹³² Mice overexpressing *AGT* only in the brain have elevated blood pressure.¹³³ The importance of a renal tubular renin-angiotensin system with angiotensinogen expressed in proximal tubular cells and renin in connecting tubular cells continues to be investigated.^{134,135}

Other phenotypes besides blood pressure may be affected by *AGT* genotype. Left ventricular mass index was found to be increased in persons with the 235T variant in a Chinese study.¹³⁶ Persons with LVH who had *AGT* 174M or 235T alleles responded to irbesartan with much greater reductions in LV mass than those with other alleles. Response to atenolol was not associated with genotype.¹³⁷ These results may explain lower LV mass in (mostly treated) hypertensives with 235 MT and TT but the reverse association in normotensives from the HyperGEN echo study.¹³⁸ In a family with a known gene causing hypertrophic cardiomyopathy, higher activity variants for several genes of the renin-angiotensin system (including *AGT* 235T) were associated with greater LV mass in cardiomyopathy gene carriers.¹³⁹ Yet another group reported a greater increase in brain infarctions associated with the 235T variant, although no association with extracranial, carotid atherosclerosis was found.¹⁴⁰ The *AGT* 235T variant has been associated with more rapid progression of immunoglobulin A nephropathy.^{141,142} One group¹⁴³ reported more rapid progression to end-stage renal disease in diabetics with the 235T variant while another did not.¹⁴⁴

Consistent with the notion that the -6A (or 235T) allele of *AGT* results in increased tissue expression of angiotensinogen, we found that both normotensive homozygous carriers of the 235T *AGT* variant (most with a positive family history of hypertension)¹⁴⁵ and hypertensive patients with the -6AA genotype¹⁴⁶ showed significant blunting of renal vascular response to infused angiotensin II. This blunting (less than usual reduction of renal blood flow in response to infused angiotensin II on a high salt diet) is presumably the result of higher intrarenal angiotensin II production resulting in downregulation of vascular angiotensin II receptors. There was also blunting of the normal stimulation of adrenal aldosterone production by infused angiotensin II on a low salt diet in hypertensive patients with the *AGT* -6AA genotype.¹⁴⁶ Interestingly, there was no association between *AGT* genotype and blood pressure response to salt change in our studies (comparing blood pressures at the end of one week on 200 mEq sodium per day and 1 week on 10 mEq/day) (unpublished observations, 2003). In one study of normotensive and hypertensive persons over age 60, the *AGT* 235T genotype was associated with a lesser diastolic response to changes in salt intake.¹⁴⁷ These results may suggest that the ability of the renin-angiotensin system to respond to marked changes in salt over a relatively short time remains intact with the relatively modest effects of the -6A variant. Nevertheless, 2 long-term intervention studies including a reduction of salt intake^{148,149} and one study utilizing increased fruit and vegetable intake¹⁵⁰ have noted greater responses to the intervention in persons with the -6AA

tive in treating overproduction of angiotensinogen restricted to the kidney. Intravenous injection of antisense oligonucleotides into spontaneously hypertensive rats resulted in reduction in plasma angiotensinogen, angiotensin II, and blood

genotype. Those with the -6GG genotype had the least response, whereas heterozygotes were intermediate.

In summary, findings to date suggest that the -6A allele of *AGT* is a marker for greater risk of hypertension and better response to dietary intervention. However consistent these findings are, it would be premature at this time for a clinician to alter recommendations for prevention or treatment based on *AGT* genotype.

Other genes of the renin-angiotensin system

Variants in the renin gene have apparently not been linked or associated with human hypertension.^{151,152} Initially, angiotensin-converting enzyme (*ACE*) seemed similarly unlinked to hypertension.¹⁵³ Most subsequent studies also failed to find associations between the *ACE* I/D variant and hypertension.¹⁵⁴ Occasional studies continue to find increased pressure in those with the DD genotype, which does display greater *ACE* activity.¹⁵⁵ More recently, however, evidence for association of the *ACE* I/D variant have emerged in the context of interaction. Thus, associations of the DD genotype with hypertension are reported for men but not women¹⁵⁶ and in the context of higher risk variants of angiotensinogen,^{119,157,158} α -adducin,^{159,160} and aldosterone synthase.¹⁶⁰ Other variants of *ACE* may also affect activity and blood pressure association.¹⁶¹ *ACE* DD genotype was associated with greater left ventricular mass index in endurance-trained athletes.¹⁶²

Genetic association or linkage with hypertension as well as mechanistic evidence has also been reported for variants of the angiotensin type 1 (AT1) receptor,^{163,164} 11 β -hydroxysteroid dehydrogenase (particularly with salt-sensitivity),^{165–167} and aldosterone synthase (*CYP11B2*).^{168–172}

α -Adducin (*ADD1*)

Unlike the development of hypotheses and observations relative to *AGT* that began as a systematic examination of genes of the renin-angiotensin system for linkage and association in humans, hypotheses relating to a role for adducin in hypertension began with studies in an animal model of hypertension. Pathophysiological studies in the Milan hypertensive rat, a salt-sensitive strain with mild hypertension, identified modestly increased proximal tubular sodium reabsorption due to increased activity of the Na⁺-K⁺ ATPase as a fundamental defect. Further detailed studies led to identification of variants in both the α and β subunits of adducin that accounted for 50% of the difference in systolic blood pressure between Milan hypertensive rats and normotensive strains. Adducin is a cytoskeletal protein that interacts with Na⁺-K⁺ ATPase. Adducin variants associated with both rat and human hypertension show greater affinity for Na⁺-K⁺ ATPase resulting in increased membrane expression and activity of Na⁺-K⁺ ATPase.^{173,174} Initial positive association studies in humans¹⁷⁵ were followed by significant linkage in hypertensive siblings¹⁷⁶ and identification of a Gly460Trp variant (with an allele frequency of 0.13–0.16 in controls) associated with hypertension.

Subsequent association studies have been reminiscent of findings after the discovery of the *AGT* association, with mixed but generally positive findings, especially for Caucasian popula-

tions.¹⁷⁷ Our own findings support the association of *ADD1* Gly460Trp with hypertension, with an approximately 50% to 70% increase in risk in Caucasians carrying the 460Trp variant, increasing to an odds ratio of 4.2 in older, heavier persons with higher triglycerides; no effects were seen in African-Americans.¹⁰²

Pathophysiological studies in humans are consistent with a significant increase in salt retention associated with the *ADD1* 460Trp variant. Thus, greater reductions in blood pressure in response to a diuretic¹⁷⁶ and greater increases in blood pressure after a saline load¹⁵⁹ were seen in 460Trp carriers. Carriers also showed lower fractional excretion of sodium and a flattened pressure-natriuresis curve.¹⁷⁸ Finally, 460Trp homozygotes more frequently had low-renin hypertension and displayed greater fraction sodium reabsorption.^{179,180}

Effects of the *ADD1* gene on blood pressure appear to interact strongly with other genes. The increase in blood pressure after a salt load was much greater in carriers of the 460Trp *ADD1* variant who also had the *ACE* DD genotype than in those with the *ACE* II genotype. *ACE* genotype had no effect (or possibly reverse effect) in those homozygous for the more common 460Gly variant.¹⁵⁹ A prospective study suggests a similar interaction affecting the risk of incident hypertension.¹⁶⁰

Other phenotypes may be affected by *ADD1* variants. Presence of *ADD1* 460Trp was associated with an approximate 2.5-fold increased risk of CAD or peripheral artery disease in a prospective follow-up of hypertensive patients. The risk was not seen in normotensive subjects.¹⁸¹ In a case-control study, diuretic therapy was associated with a 50% reduction in MI and stroke in 460Trp carriers; noncarriers had no risk reduction associated with diuretic use.¹⁸² Risk of left ventricular hypertrophy was increased 15-fold in 460Trp homozygotes.¹⁸³ Interestingly, increased salt intake has also been strongly associated with increased cardiovascular morbidity and mortality¹⁸⁴ and left ventricle mass¹⁸⁵ independent of blood pressure. Furthermore, salt-sensitivity has also been associated with greater total mortality independent of blood pressure.¹⁸⁶

Other genes affecting ion transporter activity

Variants of the endothelial sodium channel initially were not associated with essential hypertension,¹⁰⁹ but more recent studies have found some association^{187,188} or linkage.¹⁸⁹ Hypertensive black Africans with the Thr594Met variant (found in about 5% and associated with hypertension in a previous study) were highly responsive to amiloride.¹⁹⁰ Approximately 7% (10 of 139 tested) of hypertension in blacks was attributable to the Arg563Gln mutation of endothelial sodium channel in one study.¹⁹¹ Other ion transporter genes, although involving Mendelian forms of hypertension or hypotension, have apparently not been associated directly with essential hypertension. Apparently, no studies have identified associations or linkage to hypertension for the major Na-H exchanger genes *NHE1*, *NHE2*, or *NHE3* (predominates in renal proximal tubule).

An indirect association exists between the renal dopamine system and ion transport. The renal dopamine system may be considered apart from the sympathetic nervous system in that

kidney dopamine is synthesized independently of nerve activity. Proximal tubule cells synthesize dopamine from L-DOPA in tubular fluid. Synthesis of dopamine is increased by a high-sodium diet and is also strongly influenced by delivery rate of L-DOPA in filtered fluid in the proximal tubule. Dopamine, by way of the dopamine D₁ receptor, downregulates sodium transport by NHE3 in the apical membrane through cAMP-mediated effects and also downregulates Na⁺-K⁺ ATPase through diacylglycerol and PKC-mediated effects.¹⁹² The D₁ receptor has other intracellular effects and there are other dopamine receptors.¹⁹³ Of particular interest are observations of defective receptor coupling associated with increased D₁ receptor serine phosphorylation in both spontaneously hypertensive rats and humans with essential hypertension.¹⁹⁴ This increased receptor phosphorylation (resulting in uncoupling of the D₁ receptor from downstream adenylate cyclase activation) was later traced to increased activity of G protein–coupled receptor kinase 4 (GRK4γ).¹⁹⁵ In particular, several variants of the γ subunit of GRK4 showed increased activity by biochemical measures and in transgenic mice. Cursory data in human populations suggested increased risk for hypertension associated with several GRK4γ variants all showing higher than normal activity.¹⁹⁵ Significant interaction between variants of GRK4γ (termed “FJ” in this study) and variants of the renin-angiotensin system was also found¹⁵⁸ with reportedly high prediction of hypertension status using combinations of genotypes.¹⁹⁶ There are reports of variants in the D₁ and D₂ receptor genes being associated with hypertension.^{197,198}

G-protein β3 subunit (GNB3)

Numerous investigations, including some of our own,²⁸ had pointed to elevations in sodium-lithium counter-transport or Na-H exchange associated with hypertension. Siffert et al.¹⁹⁹ immortalized lymphocytes from hypertensive patients with high Na-H exchanger activity and normotensives with low activity. Cells derived from the hypertensives showed persistently greater Na-H exchange, cell proliferation, calcium transients, and inositol phosphate generation in response to agonists such as PAF and somatostatin, all suppressible by pertussis toxin, pointing to a G protein as the source of the enhanced response. No differences in receptor or G-protein number were identified, but increased binding of GTP to G proteins was observed. A variant, 825C>T, was soon identified in the GNB3 gene that did not affect the serine encoded and that was either associated with another variant or somehow affected an alternative splice site. A fraction of the clones with either CT or TT genotypes (139 of 498 clones) produced a shorter mRNA (*Gβ3-second*) with enhanced signal transduction activity. None of the CC genotype clones produced *Gβ3-second*. Further, the 825T variant was associated with hypertension in 426 hypertensive subjects versus 427 controls.²⁰⁰ Additional association studies to date have, not unexpectedly, been mixed with both positive^{201–205} and nonsignificant^{206–208} studies in Caucasian populations where 825T gene frequency is about 25%. Increased risk of hypertension associated with 825T was also reported among blacks²⁰⁹ who have a much higher gene frequency approaching

80%. A negative study was reported in African Americans.²¹⁰ Less association has been reported in Asian populations, which have intermediate gene frequencies of about 50%,^{211–213} although one Japanese study was weakly positive.²¹⁴ Greater reduction in blood pressure in response to diuretics was associated with 825T genotype.²¹⁵ However, no association was seen between 825T and blood pressure response to change in salt intake in young, normotensive men.²¹⁶ Accelerated loss of allograft function in 825T carriers was associated with an exaggeration of posttransplant hypertension.²¹⁷

A number of other variants have been identified that are in linkage disequilibrium with 825T.²¹⁸ A strong association was seen between 825T and the generation, through an alternate splice site, of yet another short variant of GNB3 (*Gβ3-second2*), which also showed greater signal transduction activity.²¹⁹ The precise mechanism explaining the strong association of 825T and the shorter variants has not yet been elucidated. The fact that only a minority of clones expressed the *Gβ3-second* variant suggests, perhaps, that there exists another linked site or sites in the gene that control expression.

In addition to associations with hypertension, the 825T variant of GNB3 is associated with overweight^{220,221} and insulin resistance.^{222,223} Subtly reduced lipolysis in adipocytes in response to isoproterenol may help explain the association with overweight.²²⁴ Other associations with the 825T variant include enhanced vasoconstriction in response to endothelin-1, norepinephrine, and angiotensin II,²²⁵ but not an α-2 agonist²²⁶ and a substantially increased response to sildenafil.²²⁷ Radial artery hypertrophy was 3 times more frequent ($P < 0.001$) in a healthy population carrying the 825T variant.²²⁸ An increased heart stroke volume in young, normotensive volunteers was reported.²²⁶ Other associations include more carotid atherosclerosis,²²³ increased risk of stroke,²²⁹ variably increased LV mass,^{230,231} and impaired diastolic filling.²³²

Other genes of the adrenergic system

Genome-wide scans have now reported linkage to one or more sites on virtually every chromosome.²³³ In one of these scans, investigators noted that the β₂-adrenergic receptor was a candidate under one of the peaks (a positional candidate gene approach). An Arg16Gly variant was found to be associated with a significant 1.8-fold increase risk of hypertension.²³⁴ Confirmatory results for this variant have been reported in other populations^{235,236} as well as a negative study.²³⁷ Attenuation of the vasodilatory response in humans with the Gly16 allele provides biological plausibility.²³⁸ Evidence for association of hypertension with variants of the β₁²³⁹ and β₃-adrenergic receptors^{104,240} has also been published. A polymorphism in the G_s-protein α-subunit (GNAS1) involved in transduction of signals from β-adrenergic receptors has been associated with hypertension and response to beta-blockers.²⁴¹

Other candidate genes

Numerous other genes, particularly those affecting vasoconstriction, may be hypothesized as candidate genes. There is conflicting evidence for effects of variants of endothelial nitric oxide synthase (NOS3) with both positive^{242–244} and nega-

tive^{245–247} association studies. Persons with the CC genotype of a $-786T>C$ variant had higher blood pressure and were more than twice as likely to be hypertensive.²⁴⁸ However, our own linkage studies were negative²⁴⁹ as were others.^{250,251}

Several studies find reduced urinary kallikrein in association with human hypertension and multiple studies support a role for kallikrein produced in the connecting tubule of the kidney (through local generation of kinin and bradykinin) in promoting diuresis and natriuresis in the face of a high salt intake.²⁵² Nevertheless, linkage and association studies of human hypertension have generally been negative for tissue kallikrein (*KLK1*) and other genes of the renal kallikrein system.^{247,253} Furthermore, a recently identified variant causing marked decrease in kallikrein activity was not associated with increased blood pressure.²⁵⁴ Potentially, other factors, such as dietary potassium intake, may interact to modify associations with urinary kallikrein.²⁵⁵ Whereas gene delivery of human tissue kallikrein reduced blood pressure in spontaneously hypertensive rats,²⁵⁶ mice made deficient in either the bradykinin receptor-2 or tissue kallikrein were not hypertensive.²⁵⁷ Further work will be required to provide further clarification of the role, if any, of the renal kallikrein-kinin system in hypertension.

There was little relationship between plasma levels of atrial natriuretic peptide and blood pressures, risk of hypertension, or family history of hypertension in 301 families studied in Rochester, Minnesota.²⁵⁸ Association studies with variants of the atrial natriuretic peptide gene have also been inconsistent.^{259–261} Nevertheless, there is evidence for association between blood pressure, left ventricular hypertrophy, and variants in the atrial natriuretic peptide receptor.^{261,262} Further examination of this receptor for associations seems warranted.²⁶³ As noted in the section on multiple metabolic syndrome, endothelin-1 gene may be associated with hypertension in the context of overweight. A mutation resulting in a truncation of the prostacyclin synthase gene appeared to result in hypertension in at least one Japanese family.²⁶⁴

IMPLICATIONS FOR THE MANAGEMENT OF HYPERTENSION

Improved surveillance and treatment of hypertension continues to be a major need. Indeed, <40% of treated hypertensives achieve recognized goals and an unacceptable fraction remain unrecognized.^{1,265} Treatment remains essentially empirical with only limited ability to predict individual response to a given drug classes (e.g., blacks and the elderly tend to respond better to diuretics). Initial choice of antihypertensive medication is controversial, but diuretics remain an excellent first choice, particularly in light of the recent ALLHAT trial results.²⁶⁶ The clear benefit of diuretics over ACE inhibitors or calcium channel blockers with regard to congestive heart failure in ALLHAT brings to mind the excess risk of LVH for the α -adducin genotype favoring salt retention and associations with increased salt intake.^{183,185} Other drugs may be specifically

indicated based on medical circumstances (such as ACE inhibitors in congestive heart failure).²⁶⁷

It is widely recognized that individual responses to different antihypertensive medications are highly variable. The field of pharmacogenomics promises to provide tools to help identify individuals who may respond better to particular medications, but specific, clinically useful examples are few.^{233,268} The clinician should be aware of effects of certain common variants of drug metabolizing enzymes, but genetic tests are not currently available. Thus, usual doses of hydralazine can result in very high plasma levels in slow acetylators (due to a common polymorphism in *N*-acetyltransferase 2).²⁶⁸ Propranolol and metoprolol are hydroxylated by CYP2D6. Marked differences in plasma levels (17-fold for metoprolol) appear to be due to many genetic variations in CYP2D6 ranging from complete absence of activity (found in 1%–3% of Caucasians, more in Asian populations) to extremely rapid metabolizers.²⁶⁹ The clinical significance of these differences may be less than expected if very high levels are not associated with greater risk of clinical adverse events and produce no more pharmacological effects than lower doses due to saturation of receptors. Although a few instances of differential response based on genotype are noted above, none are sufficiently consistent to warrant changing recommended treatment approaches that are based on clinical trial data.^{267,270}

Summarizing the contribution of genetics to current treatment choice for the vast majority of hypertensives, there is no genetic test that contributes in a meaningful way to choice of antihypertensive drugs or diet intervention. This remains true currently despite enticing leads regarding potentially greater salt responsiveness for variants of genes such as α -adducin, ENaC, or some of the genes of the RAS. Formal randomized control trials with stratification by genotype are probably warranted, selecting participants for some of the more common, well-established variants.

Exceptions to the lack of clinical direction currently provided by genetics are the rare autosomal-dominant monogenic forms of hypertension. In particular, the blood pressure in glucocorticoid-remediable hyperaldosteronism (GRA) responds to steroid supplementation. Although routine genetic testing for these rare syndromes is not clinically available, it may be helpful to pursue genotyping through an interested research facility for families with multiple family members having very early onset, severe hypertension. Testing for abnormal urine metabolites (18-hydroxy and 18-oxocortisol steroids) may be sufficient for diagnosis of GRA.

Although gene testing in the clinical setting is currently impractical and unproven, family history remains a powerful predictor of subsequent hypertension and cardiovascular risk. The clinical work-up of any new hypertensive patient should include a careful family history including age at onset of hypertension, coronary artery disease, stroke, and diabetes, as well as some indication of body weight, smoking status, and plasma lipids for all first degree relatives. Similar information on second degree relatives can be useful as well. Such a family history is conveniently obtained by providing the patient with a form

that can be filled out in consultation with other family members before the clinical visit. Knowledge obtained from such a family history should empower the clinician and patient to be more vigilant with preventive measures not only in the patient but among his or her close relatives. Among the most important of these measures for hypertension treatment or prevention is achieving or maintaining an ideal body weight. A reduced salt diet and an abundant intake of fruits and vegetables should also be a part of the dietary advice given to persons with a strong family history of hypertension.^{267,270}

A careful family history frequently discloses familial lipid disorders in hypertensive patients. Familial dyslipidemic hypertension or familial metabolic syndrome with a predominance of moderately increased triglycerides and low HDL is the most common picture. There are important clinical implications regarding the commonplace occurrence of metabolic syndrome in the hypertensive patient. When treating hypertension, lipids must be assessed and treated aggressively. Weight loss (and increased exercise) is a desirable first step in treating dyslipidemic hypertension. Successful weight loss, even if modest, may have disproportionate benefits for the patient with metabolic syndrome. Drug treatment for lipid disorders should follow established guidelines. Most clinicians are comfortable with statins in lowering LDL, but use of fibrates or niacin is much less frequently used. Nevertheless, among those with elevated triglycerides and low HDL benefits are likely substantial.^{271–288}

References

- Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 2003;290:199–206.
- Neaton JD, Kuller L, Stamler J, Wentworth DN. Impact of systolic and diastolic blood pressure on cardiovascular mortality. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis, and management Second Edition. 2nd ed. New York: Raven Press, Ltd; 1995:127–144.
- Robertson WB, Strong JP. Atherosclerosis in persons with hypertension and diabetes mellitus. *Lab Invest* 1968;18:539–551.
- Solberg LA, McGarry PA. Cerebral atherosclerosis in persons with selected diseases. *Lab Invest* 1968;18:613–619.
- Hollander W, Madoff I, Paddock J. Aggravation of atherosclerosis by hypertension in a subhuman primate model with coarctation of the aorta. *Circ Res* 1976;38(Suppl II):63–72.
- Lopez JAG, Armstrong ML, Harrison DG, Piegoris DJ, Heistad DD. Responsiveness of iliac collateral vessels to constrictor stimuli in atherosclerotic primates. *Circ Res* 1988;63:1020–1028.
- Curmi PA, Juan L, Tedgui A. Effect of transmural pressure on low density lipoprotein and albumin transport and distribution across the intact arterial wall. *Circ Res* 1990;66:1692–1702.
- Meyer G, Merval R, Tedgui A. Effects of pressure-induced stretch and convection on low-density lipoprotein and albumin uptake in the rabbit aortic wall. *Circ Res* 1996;79:532–540.
- Glagov S, Ozoa AK. Significance of the relatively low incidence of atherosclerosis in the pulmonary, renal and mesenteric arteries. *Ann NY Acad Sci* 1968;149:940–955.
- Buja LM, Kovanen PT, Bilheimer DW. Cellular pathology of homozygous familial hypercholesterolemia. *Am J Pathol* 1979;97:327–357.
- Stehbens WE, Wierzbicki E. The relationship of hypercholesterolemia to atherosclerosis with particular emphasis on familial hypercholesterolemia, diabetes mellitus, obstructive jaundice, myxedema, and the nephrotic syndrome. *Prog Cardiovasc Dis* 1988;30:289–306.
- Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282:2035–2042.
- Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;346:1647–1653.
- Shahar E, Chambliss LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2003;34:623–631.
- Koren-Morag N, Tanne D, Graff E, Goldbourt U. Low- and high-density lipoprotein cholesterol and ischemic cerebrovascular disease: the bezafibrate infarction prevention registry. *Arch Intern Med* 2002;162:993–999.
- Amarencio P, Duyckaerts C, Tzourio C, Henin D, Bousser M-G, Hauw J-J. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. *N Engl J Med* 1992;326:221–225.
- Amarencio P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994;331:1474–1479.
- de Leeuw FE, De Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J. Aortic atherosclerosis at middle age predicts cerebral white matter lesions in the elderly. *Stroke* 2000;31:425–429.
- Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557–1562.
- Aronow WS, Ahn C. Incidence of heart failure in 2,737 older persons with and without diabetes mellitus. *Chest* 1999;115:867–868.
- Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988;108:7–13.
- Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561–1566.
- Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and hemorrhagic stroke in men: Korea Medical Insurance Corporation Study. *Lancet* 2001;357:922–925.
- Flaxman N. The course of hypertensive heart disease, 1: Age of onset development of cardiac insufficiency, duration of life, and cause of death. *Ann Intern Med* 1936;10:748–753.
- Luft FC. Hypertension as a complex genetic trait. *Semin Nephrol* 2002;22:115–126.
- Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. *J Chron Dis* 1986;39:809–821.
- Hunt SC, Hasstedt SJ, Kuida H, Stults BM, Hopkins PN, Williams RR. Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. *Am J Epidemiol* 1989;129:625–638.
- Williams RR, Hasstedt SJ, Hunt SC, Wu LL, Hopkins PN, Berry TD et al. Genetic traits related to hypertension and electrolyte metabolism. *Hypertension* 1991;17(suppl I):I-69–I-73.
- Ward R. Familial aggregation and genetic epidemiology of blood pressure. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press, Ltd; 1995:67–88.
- Hasstedt SJ, Wu LL, Ash KO, Kuida H, Williams RR. Hypertension and sodium-lithium countertransport in Utah pedigrees: Evidence for major-locus inheritance. *Am J Hum Genet* 1988;43:14–22.
- Chien KL, Yang CY, Lee YT. Major gene effects in systolic and diastolic blood pressure in families receiving a health examination in Taiwan. *J Hypertens* 2003;21:73–79.
- Rubattu S, Volpe M, Kreutz R, Ganter U, Ganter D, Lindpaintner K. Chromosomal mapping of quantitative trait loci contributing to stroke in a rat model of complex human disease. *Nat Genet* 1996;13:429–434.
- Rubattu S, Ridker P, Stampfer MJ, Volpe M, Hemmekens CH, Lindpaintner K. The gene encoding atrial natriuretic peptide and the risk of human stroke. *Circulation* 1999;100:1722–1726.
- Palsdottir A, Abrahamsen M, Thorsteinsson L, Arnason A, Olafsson I, Grubb A et al. Mutation in cystatin C gene causes hereditary brain haemorrhage. *Lancet* 1988;2:603–604.
- Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383(6602):707–710.
- Dong Y, Hassan A, Zhang Z, Huber D, Dalageorgou C, Markus HS. Yield of screening for CADASIL mutations in lacunar stroke and leukoaraiosis. *Stroke* 2003;34:203–205.
- Wardlaw JM, Sandercock PA, Dennis MS, Starr J, Kalimo H. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003;34:806–812.
- Carmelli D, DeCarli C, Swan GE, Jack LM, Reed T, Wolf PA et al. Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. *Stroke* 1998;29:1177–1181.
- de Faire U, Friberg L, Lundman T. Concordance for mortality with special reference to ischaemic heart disease and cerebrovascular disease: A study on the Swedish Twin Registry. *Prev Med* 1975;4:509–517.

40. Welin L, Svardsudd K, Wilhelmsen L, Larsson B, Tibblin G. Analysis of risk factors for stroke in a cohort of men born in 1913. *N Engl J Med* 1987;317:521–526.
41. Bak S, Gaist D, Sindrup SH, Skytte A, Christensen K. Genetic liability in stroke: a long-term follow-up study of Danish twins. *Stroke* 2002;33:769–774.
42. Gretarsdottir S, Steinbjornsson S, Jonsson HH, Jakobsson F, Einarsdottir E, Agnarsson U et al. Localization of a susceptibility gene for common forms of stroke to 5q12. *Am J Hum Genet* 2002;70:593–603.
43. Woo D, Sauerbeck LR, Kissela BM, Khouri JC, Szaflarski JP, Gebel J et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. *Stroke* 2002;33:1190–1195.
44. Okamoto K, Horisawa R, Kawamura T, Asai A, Ogino M, Takagi T et al. Family history and risk of subarachnoid hemorrhage: a case-control study in nagoya, Japan. *Stroke* 2003;34:422–426.
45. Garner C, Lecomte E, Visvikis S, Abergel E, Lathrop M, Soubrier F. Genetic and environmental influences on left ventricular mass. A family study. *Hypertension* 2000;36:740–746.
46. Tang W, Arnett DK, Devereux RB, Province MA, Atwood LD, Oberman A et al. Sibling resemblance for left ventricular structure, contractility, and diastolic filling. *Hypertension* 2002;40:233–238.
47. Jeanclous E, Schork NJ, Kyvik KO, Kimura M, Skurnick JH, Aviv A. Telomere length inversely correlates with pulse pressure and is highly familial. *Hypertension* 2000;36:195–200.
48. Jartti L, Ronnemaa T, Kaprio J, Jarvisalo MJ, Toikka JO, Marniemi J et al. Population-based twin study of the effects of migration from Finland to Sweden on endothelial function and intima-media thickness. *Arterioscler Thromb Vasc Biol* 2002;22:832–837.
49. Lange LA, Bowden DW, Langefeld CD, Wagenknecht LE, Carr JJ, Rich SS et al. Heritability of carotid artery intima-medial thickness in type 2 diabetes. *Stroke* 2002;33:1876–1881.
50. Xiang AH, Azen SP, Buchanan TA, Raffel LJ, Tan S, Cheng LS et al. Heritability of subclinical atherosclerosis in Latino families ascertained through a hypertensive parent. *Arterioscler Thromb Vasc Biol* 2002;22:843–848.
51. Fox CS, Polak JF, Chazaro I, Cupples A, Wolf PA, D'Agostino RA et al. Genetic and environmental contributions to atherosclerosis phenotypes in men and women: heritability of carotid intima-media thickness in the Framingham Heart Study. *Stroke* 2003;34:397–401.
52. Hunt KJ, Duggirala R, Gorling HH, Williams JT, Almasy L, Blangero J et al. Genetic basis of variation in carotid artery plaque in the San Antonio Family Heart Study. *Stroke* 2002;33:2775–2780.
53. Jerrard-Dunne P, Sitzer M, Risley P, Steckel DA, Buehler A, Von Kegler S et al. Interleukin-6 Promoter Polymorphism Modulates the Effects of Heavy Alcohol Consumption on Early Carotid Artery Atherosclerosis: The Carotid Atherosclerosis Progression Study (CAPS). *Stroke* 2003;34:402–407.
54. Zannad F, Benetos A. Genetics of intima-media thickness. *Curr Opin Lipidol* 2003;14:191–200.
55. Perusse L, Moll PP, Sing CF. Evidence that a single gene with gender- and age-dependent effects influences systolic blood pressure determination in a population-based sample. *Am J Hum Genet* 1991;49:94–105.
56. Cheng LS-C, Carmelli D, Hunt SC, Williams RR. Evidence for a major gene influencing 7-year increases in diastolic blood pressure with age. *Am J Hum Genet* 1995;57:1169–1177.
57. Denton D, Weisinger R, Mundy N, Wickings EJ, Dixson A, Moisson P et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nature Med* 1995;1:1009–1016.
58. INTERSALT Cooperative Research Group. INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;297:319–328.
59. Garrison RJ, Kannel WB, Stokes J, Castelli WP. Incidence and precursors of hypertension in young adults: The Framingham Offspring Study. *Prev Med* 1987;16:235–251.
60. Cooper R, Rotimi C, Ataman S, McGee D, Osotimehin B, Kadiri S et al. The prevalence of hypertension in seven populations of West African origin. *Am J Public Health* 1997;87:160–168.
61. MacGregor GA. Sodium is more important than calcium in essential hypertension. *Hypertension* 1985;7:628–637.
62. Hollenberg NK, Martinez G, McCullough M, Meinking T, Passan D, Preston M et al. Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. *Hypertension* 1997;29:171–176.
63. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure: Less of one, more of the other? *Am J Hypertens* 1988;1(Pt 1):335–347.
64. Clark AT, Bertram JF. Molecular regulation of nephron endowment. *Am J Physiol* 1999;276(Pt 2):F485–F497.
65. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 2000;58:770–773.
66. Vehaskari VM, Aviles DH, Manning J. Prenatal programming of adult hypertension in the rat. *Kidney Int* 2001;59:238–245.
67. Cullen-McEwen LA, Kett MM, Dowling J, Anderson WP, Bertram JF. Nephron number, renal function, and arterial pressure in aged GDNF heterozygous mice. *Hypertension* 2003;41:335–340.
68. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003;348:101–108.
69. Guyton AC, Hall JE, Coleman TG, Manning RD, Norman RA. The dominant role of the kidney in long-term arterial pressure regulation in normal and hypertensive states. In: Laragh JH, Brenner BM, eds. *Hypertension: pathophysiology, diagnosis, and management*. 2nd ed. New York: Raven Press, Ltd.; 1995:1311–1326.
70. Guyton AC, Coleman TG. Quantitative analysis of the pathophysiology of hypertension. *Circ Res* 1969;24(5 Suppl):1–19.
71. Guyton A, Coleman T, Cowley A. Arterial pressure regulation: Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972;52:584–594.
72. Guyton A, Coleman T, Cowley A. A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. *Circ Res* 1974;35:159–176.
73. Guyton AC. Circulatory physiology III: Arterial pressure and hypertension. Philadelphia: W.B. Saunders Company; 1980;
74. Barlassina C, Lanzani C, Manunta P, Bianchi G. Genetics of essential hypertension: from families to genes. *J Am Soc Nephrol* 2002;13 Suppl 3:S155–S164.
75. Lalouel JM, Rohrwaßer A. Development of genetic hypotheses in essential hypertension. *J Hum Genet* 2001;46:299–306.
76. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;104:545–556.
77. Williams RR, Hunt SC, Hopkins PN, Stults BM, Wu LL, Hasstedt SJ et al. Familial dyslipidemic hypertension. Evidence from 58 Utah families for a syndrome present in approximately 12% of patients with essential hypertension. *JAMA* 1988;259:3579–3586.
78. Hopkins PN, Hunt SC, Wu LL, Williams GH, Williams RR. Hypertension, dyslipidemia, and insulin resistance: links in a chain or spokes on a wheel? *Curr Opin Lipidol* 1996;7:241–253.
79. Selby JV, Newman B, Quiroga J, Christian JC, Austin MA, Fabsitz RR. Concordance for dyslipidemic hypertension in male twins. *JAMA* 1991;265:2079–2084.
80. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA et al. Blood pressure, stroke, and coronary heart disease. Part 2. short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827–838.
81. Samuelsson O, Wilhelmsen L, Andersson OK, Pennert K, Berglund G. Cardiovascular morbidity in relation to change in blood pressure and serum cholesterol levels in treated hypertension: Results from the primary prevention trial in Goteborg, Sweden. *JAMA* 1987;258:1768–1776.
82. Hong Y, Pedersen NL, Brismar K, de Faire U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. *Am J Hum Genet* 1997;60:143–152.
83. Kronenberg F, Rich SS, Sholinsky P, Arnett DK, Province ME, Myers RH et al. Insulin and hypertension in the NHLBI Family Heart Study: a sibpair approach to a controversial issue. *Am J Hypertens* 2000;13:240–250.
84. Pausova Z, Gossard F, Gaudet D, Tremblay J, Kotchen TA, Cowley AW et al. Heritability estimates of obesity measures in siblings with and without hypertension. *Hypertension* 2001;38:41–47.
85. Egan BM, Greene EL, Goodfriend TL. Insulin resistance and cardiovascular disease. *Am J Hypertens* 2001;14 (June suppl)(6 Pt 2):116S–25S.
86. Mahamat A, Richard F, Arveiler D, Bongard V, Yarnell J, Ducimetiere P et al. Body mass index, hypertension and 5-year coronary heart disease incidence in middle aged men: the PRIME study. *J Hypertens* 2003;21:519–524.
87. Kim JK, Fillmore JJ, Chen Y, Yu C, Moore IK, Pypaert M et al. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci U S A* 2001;98:7522–7527.
88. Unger RH. Lipotoxic diseases. *Annu Rev Med* 2002;53:319–336.
89. Schaffer JE. Lipotoxicity: when tissues overeat. *Curr Opin Lipidol* 2003;14:281–287.
90. Cheng LS, Davis RC, Raffel LJ, Xiang AH, Wang N, Quinones M et al. Coincident linkage of fasting plasma insulin and blood pressure to chromosome 7q in hypertensive hispanic families. *Circulation* 2001;104:1255–1260.
91. Pajukanta P, Terwilliger JD, Perola M, Hiekkalinna T, Nuotio I, Ellonen P et al. Genomewide scan for familial combined hyperlipidemia genes in Finnish families, suggesting multiple susceptibility loci influencing triglyceride, cholesterol, and apolipoprotein B levels. *Am J Hum Genet* 1999;64:1453–1463.

92. Coon H, Myers RH, Borecki IB, Arnett DK, Hunt SC, Province MA et al. Replication of linkage of familial combined hyperlipidemia to chromosome 1q with additional heterogeneous effect of apolipoprotein A-I/C-III/A-IV locus : the NHLBI family heart study. *Arterioscler Thromb Vasc Biol* 2000;20:2275–2280.
93. Pei W, Baron H, Muller-Myhsok B, Knoblauch H, Al-Yahyaee SA, Hui R et al. Support for linkage of familial combined hyperlipidemia to chromosome 1q21-q23 in Chinese and German families. *Clin Genet* 2000;57:29–34.
94. Elbein SC, Hoffman MD, Teng K, Leppert MF, Hasstedt SJ. A genome-wide search for type 2 diabetes susceptibility genes in Utah Caucasians. *Diabetes* 1999;48:1175–1182.
95. Krushkal J, Ferrell R, Mockrin SC, Turner ST, Sing CF, Boerwinkle E. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. *Circulation* 1999;99:1407–1410.
96. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H et al. Evidence for a gene influencing blood pressure on chromosome 17 : genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension* 2000;36:477–483.
97. Hunt SC, Ellison RC, Atwood LD, Pankow JS, Province MA, Leppert MF. Genome scans for blood pressure and hypertension: the National Heart, Lung, and Blood Institute Family Heart Study. *Hypertension* 2002;40:1–6.
98. Allayee H, de Bruin TW, Michelle Dominguez K, Cheng LS, Ipp E, Cantor RM et al. Genome scan for blood pressure in Dutch dyslipidemic families reveals linkage to a locus on chromosome 4p. *Hypertension* 2001;38:773–778.
99. Tiret L, Poirier O, Hallet V, McDonagh TA, Morrison C, McMurray JJ et al. The Lys198Asn polymorphism in the endothelin-1 gene is associated with blood pressure in overweight people. *Hypertension* 1999;33:1169–1174.
100. Asai T, Ohkubo T, Katsuya T, Higaki J, Fu Y, Fukuda M et al. Endothelin-1 gene variant associates with blood pressure in obese Japanese subjects: the Ohasama Study. *Hypertension* 2001;38:1321–1324.
101. Jin JJ, Nakura J, Wu Z, Yamamoto M, Abe M, Tabara Y et al. Association of endothelin-1 gene variant with hypertension. *Hypertension* 2003;41:163–167.
102. Province MA, Arnett DK, Hunt SC, Leidecker-Foster C, Eckfeldt JH, Oberman A et al. Association between the alpha-adducin gene and hypertension in the HyperGEN Study. *Am J Hypertens* 2000;13(Pt 1):710–718.
103. Iwai N, Katsuya T, Mannami T, Higaki J, Ogihara T, Kokame K et al. Association Between SAH, an acyl-CoA synthetase gene, and hypertriglyceridemia, obesity, and hypertension. *Circulation* 2002;105:41–47.
104. Ringel J, Kreutz R, Distler A, Sharma AM. The Trp64Arg polymorphism of the beta2-adrenergic receptor gene is associated with hypertension in men with type 2 diabetes mellitus. *Am J Hypertens* 2000;13:1027–1031.
105. Lalouel JM. Large-scale search for genes predisposing to essential hypertension. *Am J Hypertens* 2003;16:163–166.
106. Samani NJ. Genome scans for hypertension and blood pressure regulation. *Am J Hypertens* 2003;16:167–171.
107. Meneton P. Comparative roles of the renal apical sodium transport systems in blood pressure control. *J Am Soc Nephrol* 2000;11 Suppl 16:S135–S139.
108. Doris PA. Hypertension genetics, single nucleotide polymorphisms, and the common disease/common variant hypothesis. *Hypertension* 2002;39(Pt 2):323–331.
109. Corvol P, Persu A, Gimenez-Roqueplo AP, Jeunemaitre X. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. *Hypertension* 1999;33:1324–1331.
110. Jeunemaitre X, Soubrier F, Kotlevtsev YV, Lifton RP, Williams CS, Charru A et al. Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992;71:169–180.
111. Staessen JA, Kuznetsova T, Wang JG, Emelianov D, Vlietinck R, Fagard R. M235T angiotensinogen gene polymorphism and cardiovascular renal risk. *J Hypertens* 1999;17:9–17.
112. Inoue I, Nakajima T, Williams CS, Quackenbush J, Puryear R, Powers M et al. A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription in vitro. *J Clin Invest* 1997;99:1786–1797.
113. Province MA, Boerwinkle E, Chakravarti A, Cooper R, Fornage M, Leppert M et al. Lack of association of the angiotensinogen-6 polymorphism with blood pressure levels in the comprehensive NHLBI Family Blood Pressure Program. National Heart, Lung and Blood Institute. *J Hypertens* 2000;18:867–876.
114. Rankinen T, Gagnon J, Perusse L, Rice T, Leon AS, Skinner JS et al. Body fat, resting and exercise blood pressure and the angiotensinogen M235T polymorphism: the HERITAGE family study. *Obes Res* 1999;7:423–430.
115. Iso H, Harada S, Shimamoto T, Sato S, Kitamura A, Sankai T et al. Angiotensinogen T174M and M235T variants, sodium intake and hypertension among non-drinking, lean Japanese men and women. *J Hypertens* 2000;18:1197–1206.
116. Ishikawa K, Baba S, Katsuya T, Iwai N, Asai T, Fukuda M et al. T+31C polymorphism of angiotensinogen gene and essential hypertension. *Hypertension* 2001;37:281–5.
117. Tiago AD, Samani NJ, Candy GP, Brookbank R, Libhaber EN, Sareli P et al. Angiotensinogen gene promoter region variant modifies body size-ambulatory blood pressure relations in hypertension. *Circulation* 2002;106:1483–1487.
118. Pereira AC, Mota GF, Cunha RS, Herbenhoff FL, Mill JG, Krieger JE. Angiotensinogen 235T allele “dosage” is associated with blood pressure phenotypes. *Hypertension* 2003;41:25–30.
119. Tsai CT, Fallin D, Chiang FT, Hwang JJ, Lai LP, Hsu KL et al. Angiotensinogen gene haplotype and hypertension: interaction with ACE gene I allele. *Hypertension* 2003; 41:9–15.
120. Hingorani AD, Jia H, Stevens PA, Hopper R, Dickerson JE, Brown MJ. Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. *J Hypertens* 1995;13(Pt 2): 1602–1609.
121. Dudley C, Keavney B, Casadei B, Conway J, Bird R, Ratcliffe P. Prediction of patient responses to antihypertensive drugs using genetic polymorphisms: investigation of renin-angiotensin system genes. Prediction of patient responses to antihypertensive drugs using genetic polymorphisms: investigation of renin-angiotensin system genes 1996;14:259–262.
122. Lalouel JM, Rohrwitter A, Terreros D, Morgan T, Ward K. Angiotensinogen in essential hypertension: from genetics to nephrology. *J Am Soc Nephrol* 2001;12: 606–615.
123. Forrester T, McFarlane-Anderson N, Bennet F, Wilks R, Puras A, Cooper R, Rotimi C et al. Angiotensinogen and blood pressure among blacks: findings from a community survey in Jamaica. *J Hypertens* 1996;14:315–321.
124. Cooper R, Rotimi C, Ogunbiyi O, Ward R. Angiotensinogen genotype, serum level and hypertension in blacks [abstract]. *Am J Hypertens* 1997;10:33A.
125. Pratt JH, Ambrosius WT, Tewksbury DA, Wagner MA, Zhou L, Hanna MP. Serum angiotensinogen concentration in relation to gonadal hormones, body size, and genotype in growing young people. *Hypertension* 1998;32:875–879.
126. Walker WG, Whelton PK, Saito H, Russell RP, Hermann J. Relation between blood pressure and renin, renin substrate, angiotensin II, aldosterone and urinary sodium and potassium in 574 ambulatory subjects. *Hypertension* 1979;1:287–291.
127. Fardella C, Zamorano P, Mossos L, Gomez L, Pinto M, Soto J et al. A-(6)G variant of angiotensinogen gene and aldosterone levels in hypertensives. *Hypertension* 1999;34(Pt 2):779–781.
128. Kim HS, Krege JH, Kluckman KD, Hagaman JR, Hodgin JB, F. BC, Jennette JC et al. Genetic control of blood pressure and the angiotensinogen locus. *Proc Natl Acad Sci USA* 1995;92:2735–2739.
129. Smithies O, Kim HS, Takahashi N, Edgell MH. Importance of quantitative genetic variations in the etiology of hypertension. *Kidney Int* 2000;58:2265–2280.
130. Davission RL, Ding Y, Stee DE, Catterall JF, Sigmund CD. Novel mechanism of hypertension revealed by cell-specific targeting of human angiotensinogen in transgenic mice. *Physiol Genomics* 1999;1:3–9.
131. Makino N, Sugano M, Ohtsuka S, Sawada S. Intravenous injection with antisense oligodeoxynucleotides against angiotensinogen decreases blood pressure in spontaneously hypertensive rats. *Hypertension* 1998;31:1166–1170.
132. Kagiyama S, Varela A, Phillips MI, Galli SM. Antisense inhibition of brain renin-angiotensin system decreased blood pressure in chronic 2-kidney, 1 clip hypertensive rats. *Hypertension* 2001;37(Part 2):371–375.
133. Morimoto S, Cassell MD, Beltz TG, Johnson AK, Davission RL, Sigmund CD. Elevated blood pressure in transgenic mice with brain-specific expression of human angiotensinogen driven by the glial fibrillary acidic protein promoter. *Circ Res* 2001;89:365–372.
134. Rohrwitter A, Morgan T, Dillon HF, Zhao L, Callaway CW, Hillas E et al. Elements of a paracrine tubular renin-angiotensin system along the entire nephron. *Hypertension* 1999;34:1265–1274.
135. Kobori H, Nishiyama A, Harrison-Bernard LM, Navar LG. Urinary angiotensinogen as an indicator of intrarenal Angiotensin status in hypertension. *Hypertension* 2003;41:42–49.
136. Jeng JR. Left ventricular mass, carotid wall thickness, and angiotensinogen gene polymorphism in patients with hypertension. *Am J Hypertens* 1999;12:443–450.
137. Kurland L, Melhus H, Karlsson J, Kahan T, Malmqvist K, Ohman P et al. Polymorphisms in the angiotensinogen and angiotensin II type 1 receptor gene are related to change in left ventricular mass during antihypertensive treatment: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA) trial. *J Hypertens* 2002;20:657–663.
138. Tang W, Devereux RB, Rao DC, Oberman A, Hopkins PN, Kitzman DW et al. Associations between angiotensinogen gene variants and left ventricular mass and function in the HyperGEN study. *Am Heart J* 2002;143:854–860.
139. Ortlepp JR, Vosberg HP, Reith S, Ohme F, Mahon NG, Schroder D et al. Genetic polymorphisms in the renin-angiotensin-aldosterone system associated with expression of left ventricular hypertrophy in hypertrophic cardiomyopathy: a study of five polymorphic genes in a family with a disease causing mutation in the myosin binding protein C gene. *Heart* 2002;87:270–275.

140. Schmidt R, Schmidt H, Fazekas F, Launer LJ, Niederkorn K, Kapeller P et al. Angiotensinogen polymorphism M235T, carotid atherosclerosis, and small-vessel disease-related cerebral abnormalities. *Hypertension* 2001;38:110–115.
141. Pei Y, Scholey J, Thai K, Suzuki M, Catran D. Association of angiotensinogen gene T235 variant with progression of immunoglobulin A nephropathy in caucasian patients. *J Clin Invest* 1997;100:814–820.
142. Maruyama K, Yoshida M, Nishio H, Shirakawa T, Kawamura T, Tanaka R et al. Polymorphisms of renin-angiotensin system genes in childhood IgA nephropathy. *Pediatr Nephrol* 2001;16:350–355.
143. Lovati E, Richard A, Frey BM, Frey FJ, Ferrari P. Genetic polymorphisms of the renin-angiotensin-aldosterone system in end-stage renal disease. *Kidney Int* 2001;60:46–54.
144. Tomino Y, Makita Y, Shike T, Gohda T, Haneda M, Kikkawa R et al. Relationship between polymorphism in the angiotensinogen, angiotensin-converting enzyme or angiotensin II receptor and renal progression in Japanese NIDDM patients. *Nephron* 1999;82:139–144.
145. Hopkins PN, Lifton RP, Hollenberg NK, Jeunemaitre X, Hallouin MC, Skuppin J et al. Blunted renal vascular response to angiotensin II is associated with a common variant of the angiotensinogen gene and obesity. *J Hypertens* 1996;14:199–207.
146. Hopkins PN, Hunt SC, Jeunemaitre X, Smith B, Solorio D, Fisher ND et al. Angiotensinogen genotype affects renal and adrenal responses to angiotensin II in essential hypertension. *Circulation* 2002;105:1921–1927.
147. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. *J Hypertens* 2001;19:1053–1060.
148. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS et al. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: Trials of Hypertension Prevention, Phase II. *Hypertension* 1998;32:393–401.
149. Hunt SC, Geleijnse JM, Wu LL, Witteman JC, Williams RR, Grobbee DE. Enhanced blood pressure response to mild sodium reduction in subjects with the 235T variant of the angiotensinogen gene. *Am J Hypertens* 1999;12:460–466.
150. Svetkey LP, Moore TJ, Simons-Morton DG, Appel LJ, Bray GA, Sacks FM et al. Angiotensinogen genotype and blood pressure response in the Dietary Approaches to Stop Hypertension (DASH) study. *J Hypertens* 2001;19:1949–1956.
151. Jeunemaitre X, Charru A, Rigat B, Houot AM, Soubrier F, Corvol P. Sib pair linkage analysis of renin gene haplotypes in human essential hypertension. *Hum Genet* 1992;88:301–306.
152. Berge KE, Berg K. No effect of a BglI polymorphism at the renin (REN) locus on blood pressure level or variability. *Clin Genet* 1994;46:436–438.
153. Jeunemaitre X, Lifton RP, Hunt SC, Williams RR, Lalouel J-M. Absence of linkage between the angiotensin converting enzyme and human essential hypertension. *Nature Genetics* 1992;1:72–75.
154. Staessen JA, Wang JG, Ginocchio G, Petrov V, Saavedra AP, Soubrier F et al. The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. *J Hypertens* 1997;15(Pt 2):1579–1592.
155. Henskens LH, Spiering W, Stoffers HE, Soomers FL, Vlijetinck RF, de Leeuw PW et al. Effects of ACE I/D and AT1R-A1166C polymorphisms on blood pressure in a healthy normotensive primary care population: first results of the Hippocrates study. *J Hypertens* 2003;21:81–86.
156. O'Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ et al. 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* 1998;97:1766–1772.
157. Borecki IB, Province MA, Ludwig EH, Ellison RC, Folsom AR, Heiss G et al. Associations of candidate loci angiotensinogen and angiotensin-converting enzyme with severe hypertension: The NHLBI Family Heart Study. *Ann Epidemiol* 1997;7:13–21.
158. Williams SM, Addy JH, Phillips JA III, Dai M, Kpodonu J, Afful J et al. Combinations of variations in multiple genes are associated with hypertension. *Hypertension* 2000;36:2–6.
159. Barlassina C, Schork NJ, Manunta P, Citterio L, Sciarrione M, Lanella G et al. Synergistic effect of alpha-adducin and ACE genes causes blood pressure changes with body sodium and volume expansion. *Kidney Int* 2000;57:1083–1090.
160. Staessen JA, Wang JG, Brand E, Barlassina C, Birkenhager WH, Herrmann SM et al. Effects of three candidate genes on prevalence and incidence of hypertension in a Caucasian population. *J Hypertens* 2001;19:1349–1358.
161. Zhu X, Bouzakri N, Southam L, Cooper RS, Adeyemo A, McKenzie CA et al. Linkage and association analysis of angiotensin I-converting enzyme (ACE)-gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet* 2001;68:1139–1148.
162. Hernandez D, de la Rosa A, Barragan A, Barrios Y, Salido E, Torres A et al. The ACE/DD genotype is associated with the extent of exercise-induced left ventricular growth in endurance athletes. *J Am Coll Cardiol* 2003;42:527–532.
163. Kainulainen K, Perola M, Terwilliger J, Kaprio J, Koskenvuo M, Syvanen AC et al. Evidence for involvement of the type 1 angiotensin II receptor locus in essential hypertension. *Hypertension* 1999;33:844–849.
164. Duncan JA, Scholey JW, Miller JA. Angiotensin II type 1 receptor gene polymorphisms in humans: physiology and pathophysiology of the genotypes. *Curr Opin Nephrol Hypertens* 2001;10:111–116.
165. Lovati E, Ferrari P, Dick B, Jostarnadt K, Frey BM, Frey FJ et al. Molecular basis of human salt sensitivity: the role of the 11 β -hydroxysteroid dehydrogenase type 2. *J Clin Endocrinol Metab* 1999;84:3745–3749.
166. Ferrari P, Lovati E, Frey FJ. The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension. *J Hypertens* 2000;18:241–248.
167. Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de la Sierra A. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001;38:1204–1209.
168. Davies E, Holloway CD, Ingram MC, Inglis GC, Friel EC, Morrison C et al. Aldosterone excretion rate and blood pressure in essential hypertension are related to polymorphic differences in the aldosterone synthase gene CYP11B2. *Hypertension* 1999;33:703–707.
169. Tamaki S, Iwai N, Tsujita Y, Kinoshita M. Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. *Hypertension* 1999;33(Pt 2):266–270.
170. Komiyama I, Yamada T, Takara M, Asawa T, Shimabukuro M, Nishimori T et al. Lys(173)Arg and -344T/C variants of CYP11B2 in Japanese patients with low-renin hypertension. *Hypertension* 2000;35:699–703.
171. Tsukada K, Ishimitsu T, Teranishi M, Saitoh M, Yoshii M, Inada H et al. Positive association of CYP11B2 gene polymorphisms with genetic predisposition to essential hypertension. *J Hum Hypertens* 2002;16:789–793.
172. Kurland L, Melhus H, Karlsson J, Kahan T, Malmqvist K, Ohman P et al. Aldosterone synthase (CYP11B2) -344 C/T polymorphism is related to antihypertensive response: result from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVIA) trial. *Am J Hypertens* 2002;15:389–393.
173. Ferrandi M, Salardi S, Tripodi G, Barassi P, Rivera R, Manunta P et al. Evidence for an interaction between adducin and Na⁺-K⁺-ATPase: relation to genetic hypertension. *Am J Physiol* 1999;277(Pt 2):H1338–H1349.
174. Glorioso N, Filigheddu F, Cusi D, Troffa C, Conti M, Natalizio M et al. α -Adducin 460Trp allele is associated with erythrocyte Na transport rate in North Sardinian primary hypertensives. *Hypertension* 2002;39(Pt 2):357–362.
175. Casari G, Barlassina C, Cusi D, Zagato L, Muirhead R, Righetti M et al. Association of the α -adducin locus with essential hypertension. *Hypertension* 1995;25:320–326.
176. Cusi D, Barlassina C, Azzani T, Casari G, Citterio L, Devoto M et al. Polymorphisms of α -adducin and salt sensitivity in patients with essential hypertension. *Lancet* 1997;349:1353–1357.
177. Bianchi G, Cusi D. Association and linkage analysis of alpha-adducin polymorphism: is the glass half full or half empty? *Am J Hypertens* 2000;13(Pt 1):739–743.
178. Manunta P, Cusi D, Barlassina C, Righetti M, Lanzani C, D'Amico M et al. α -Adducin polymorphisms and renal sodium handling in essential hypertensive patients. *Kidney Int* 1998;53:1471–1478.
179. Grant FD, Romero JR, Jeunemaitre X, Hunt SC, Hopkins PN, Hollenberg NH et al. Low-renin hypertension, altered sodium homeostasis, and an alpha-adducin polymorphism. *Hypertension* 2002;39:191–196.
180. Sugimoto K, Hozawa A, Katsuya T, Matsubara M, Ohkubo T, Tsuji I et al. Alpha-adducin Gly460Trp polymorphism is associated with low renin hypertension in younger subjects in the Ohasama study. *J Hypertens* 2002;20:1779–1784.
181. Morrison AC, Bray MS, Folsom AR, Boerwinkle E. ADD1 460W allele associated with cardiovascular disease in hypertensive individuals. *Hypertension* 2002;39:1053–1057.
182. Psaty BM, Smith NL, Heckbert SR, Vos HL, Lemaitre RN, Reiner AP et al. Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. *JAMA* 2002;287:1680–1689.
183. Winnicki M, Somers VK, Accurso V, Hoffmann M, Pawlowski R, Frigo G et al. Alpha-Adducin Gly460Trp polymorphism, left ventricular mass and plasma renin activity. *J Hypertens* 2002;20:1771–1777.
184. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999;282:2027–2034.
185. Messerli FH, Schmieder RE, Weir MR. Salt: A perpetrator of hypertensive target organ disease? *Arch Intern Med* 1997;157:2449–2452.
186. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension* 2001;37(Part 2):429–432.
187. Baker EH, Dong YB, Sagnella GA, Rothwell M, Onipinla AK, Markandu ND et al. Association of hypertension with T594M mutation in beta subunit of epithelial sodium channels in black people resident in London. *Lancet* 1998;351:1388–1392.

188. Iwai N, Baba S, Mannami T, Ogihara T, Ogata J. Association of a sodium channel alpha subunit promoter variant with blood pressure. *J Am Soc Nephrol* 2002;13:80–85.
189. Wong ZY, Stebbing M, Ellis JA, Lamantia A, Harrap SB. Genetic linkage of beta and gamma subunits of epithelial sodium channel to systolic blood pressure. *Lancet* 1999;353:1222–1225.
190. Baker EH, Duggal A, Dong Y, Ireson NJ, Wood M, Markandu ND et al. Amiloride, a specific drug for hypertension in black people with T594M variant? *Hypertension* 2002;40:13–17.
191. Rayner BL, Owen EP, King JA, Soule SG, Vreede H, Opie LH et al. A new mutation, R563Q, of the beta subunit of the epithelial sodium channel associated with low-renin, low-aldosterone hypertension. *J Hypertens* 2003;21:921–926.
192. Carey RM. Theodore Cooper Lecture. Renal dopamine system: paracrine regulator of sodium homeostasis and blood pressure. *Hypertension* 2001;38:297–302.
193. Hussain T, Lokhandwala MF. Renal dopamine receptors and hypertension. *Exp Biol Med (Maywood)* 2003;228:134–142.
194. Sanada H, Jose PA, Hazen-Martin D, Yu PY, Xu J, Bruns DE et al. Dopamine-1 receptor coupling defect in renal proximal tubule cells in hypertension. *Hypertension* 1999;33:1036–1042.
195. Felder RA, Sanada H, Xu J, Yu PY, Wang Z, Watanabe H et al. G protein-coupled receptor kinase 4 gene variants in human essential hypertension. *Proc Natl Acad Sci U S A* 2002;99:3872–3877.
196. Jose PA, Eisner GM, Felder RA. Dopamine and the kidney: a role in hypertension? *Curr Opin Nephrol Hypertens* 2003;12:189–194.
197. Sato M, Soma M, Nakayama T, Kamimatsu K. Dopamine D1 receptor gene polymorphism is associated with essential hypertension. *Hypertension* 2000;36:183–186.
198. Rosmond R, Rankinen T, Chagnon M, Perusse L, Chagnon YC, Bouchard C et al. Polymorphism in exon 6 of the dopamine D receptor gene (DRD2) is associated with elevated blood pressure and personality disorders in men. *J Hum Hypertens* 2001;15:553–558.
199. Siffert W, Rosskopf D, Moritz A, Wieland T, Kaldenberg-Stasch S, Kettler N et al. Enhanced G protein activation in immortalized lymphoblasts from patients with essential hypertension. *J Clin Invest* 1995;96:759–66.
200. Siffert W, Rosskopf D, Siffert G, Busch S, Moritz A, Erbel R et al. Association of a human G-protein $\beta 3$ subunit variant with hypertension. *Nat Genet* 1998;18:45–48.
201. Schunkert H, Hense HW, Doring A, Rieger GA, Siffert W. Association between a polymorphism in the G protein beta3 subunit gene and lower renin and elevated diastolic blood pressure levels. *Hypertension* 1998;32:510–513.
202. Benjafield AV, Jeyasingam CL, Nyholt DR, Griffiths LR, Morris BJ. G-protein beta3 subunit gene (GNB3) variant in causation of essential hypertension. *Hypertension* 1998;32:1094–1097.
203. Beige J, Hohenbleicher H, Distler A, Sharma AM. G-Protein beta3 subunit C825T variant and ambulatory blood pressure in essential hypertension. *Hypertension* 1999;33:1049–1051.
204. Hengstenberg C, Schunkert H, Mayer B, Doring A, Lowel H, Hense HW et al. Association between a polymorphism in the G protein beta3 subunit gene (GNB3) with arterial hypertension but not with myocardial infarction. *Cardiovasc Res* 2001;49:820–827.
205. Dzida G, Golon-Siekierska P, Puzniak A, Sobstyl J, Bilan A, Mosiewicz J et al. G-protein beta3 subunit gene C825T polymorphism is associated with arterial hypertension in Polish patients with type 2 diabetes mellitus. *Med Sci Monit* 2002;8:CR597–CR602.
206. Brand E, Herrmann SM, Nicoud V, Ruidavets JB, Evans A, Arveiler D et al. The 825C/T polymorphism of the G-protein subunit beta3 is not related to hypertension. *Hypertension* 1999;33:1175–1178.
207. Buchmayer H, Sunder-Plassmann G, Hirschl MM, Kletzmayer J, Woisetschlag C, Lagner AN et al. G-protein $\beta 3$ subunit gene (GNB3) polymorphism 825C→T in patients with hypertensive crisis. *Crit Care Med* 2000;28:3203–3206.
208. Snapir A, Heinonen P, Tuomainen TP, Lakka TA, Kauhanen J, Salonen JT et al. G-protein beta3 subunit C825T polymorphism: no association with risk for hypertension and obesity. *J Hypertens* 2001;19:2149–2155.
209. Dong Y, Zhu H, Sagnella GA, Carter ND, Cook DG, Cappuccio FP. Association between the C825T polymorphism of the G protein beta3-subunit gene and hypertension in blacks. *Hypertension* 1999;34:1193–1196.
210. Larson NI, Hutchinson R, Boerwinkle E. Lack of association of 3 functional gene variants with hypertension in African Americans. *Hypertension* 2000;35:1297–1300.
211. Kato N, Sugiyama T, Morita H, Kurihara H, Yamori Y, Yazaki Y. G protein beta3 subunit variant and essential hypertension in Japanese. *Hypertension* 1998;32:935–938.
212. Ishikawa K, Imai Y, Katsuya T, Ohkubo T, Tsuji I, Nagai K et al. Human G-protein $\beta 3$ subunit variant is associated with serum potassium and total cholesterol levels but not with blood pressure. *Am J Hypertens* 2000;13:140–145.
213. Tsai CH, Yeh HI, Chou Y, Liu HF, Yang TY, Wang JC et al. G protein beta3 subunit variant and essential hypertension in Taiwan - a case-control study. *Int J Cardiol* 2000;73:191–195; discussion 7–8.
214. Tozawa Y. G protein $\beta 3$ subunit variant: tendency of increasing susceptibility to hypertension in Japanese. *Blood Press* 2001;10:131–134.
215. Turner ST, Schwartz GL, Chapman AB, Boerwinkle E. C825T polymorphism of the G protein beta-subunit and antihypertensive response to a thiazide diuretic. *Hypertension* 2001;37(Part 2):739–743.
216. Schorr U, Blaschke K, Beige J, Distler A, Sharma AM. G-protein beta3 subunit 825T allele and response to dietary salt in normotensive men. *J Hypertens* 2000;18:855–859.
217. Beige J, Kreutz R, Tscherkachina I, Scherer S, Sharma AM, Zidek W et al. Matrix analysis for the dissection of interactions of G-protein $\beta 3$ subunit C825T genotype, allograft function, and posttransplant hypertension in kidney transplantation. *Am J Kidney Dis* 2002;40:1319–1324.
218. Rosskopf D, Manthey I, Siffert W. Identification and ethnic distribution of major haplotypes in the gene GNB3 encoding the G-protein beta3 subunit. *Pharmacogenetics* 2002;12:209–220.
219. Rosskopf D, Manthey I, Habich C, Kielbik M, Eisenhardt A, Nikula C et al. Identification and characterization of Gbeta3s2, a novel splice variant of the G-protein beta3 subunit. *Biochem J* 2002;Pt:
220. Siffert W, Naber C, Walla M, Ritz E. G protein $\beta 3$ subunit 825T allele and its potential association with obesity in hypertensive individuals. *J Hypertens* 1999;17:1095–1098.
221. Poston WS, Haddock CK, Spertus J, Catanese DM, Pavlik VN, Hyman DJ et al. Physical activity does not mitigate G-protein-related genetic risk for obesity in individuals of African descent. *Eat Weight Disord* 2002;7:68–71.
222. Poch E, Giner V, Gonzalez-Nunez D, Coll E, Oriola J, de la Sierra A. Association of the G protein $\beta 3$ subunit T allele with insulin resistance in essential hypertension. *Clin Exp Hypertens* 2002;24:345–353.
223. Wascher TC, Paulweber B, Malaimare L, Stadlmayr A, Iglseder B, Schmoelzer I et al. Associations of a human G protein $\beta 3$ subunit dimorphism with insulin resistance and carotid atherosclerosis. *Stroke* 2003;34:605–609.
224. Benjafield AV, Lin RC, Dalziel B, Gosby AK, Caterson ID, Morris BJ. G-protein $\beta 3$ subunit gene splice variant in obesity and overweight. *Int J Obes Relat Metab Disord* 2001;25:777–780.
225. Wenzel RR, Siffert W, Bruck H, Philipp T, Schafers RF. Enhanced vasoconstriction to endothelin-1, angiotensin II and noradrenaline in carriers of the GNB3 825T allele in the skin microcirculation. *Pharmacogenetics* 2002;12:489–495.
226. Schafers RF, Nurnberger J, Rutz A, Siffert W, Wenzel RR, Mitchell A et al. Haemodynamic characterization of young normotensive men carrying the 825T-allele of the G-protein beta3 subunit. *Pharmacogenetics* 2001;11:461–470.
227. Sperling H, Eisenhardt A, Virchow S, Hauck E, Lenk S, Porst H et al. Sildenafil response is influenced by the G protein beta 3 subunit GNB3 C825T polymorphism: a pilot study. *J Urol* 2003;169:1048–1051.
228. Hanon O, Luong V, Mourad JJ, Bortolotto LA, Safar M, Girerd X. Association between the G protein beta3 subunit 825t allele and radial artery hypertrophy. *J Vasc Res* 2002;39:497–503.
229. Morrison AC, Doris PA, Folsom AR, Nieto FJ, Boerwinkle E. G-protein beta3 subunit and alpha-adducin polymorphisms and risk of subclinical and clinical stroke. *Stroke* 2001;32:822–829.
230. Sempricini A, Siffert W, Sartori M, Monari A, Naber C, Frigo G et al. G protein $\beta 3$ subunit gene 825T allele is associated with increased left ventricular mass in young subjects with mild hypertension. *Am J Hypertens* 2001;14:1191–1195.
231. Sedlacek K, Fischer M, Erdmann J, Hengstenberg C, Holmer S, Kurzinger S et al. Relation of the G protein beta3-subunit polymorphism with left ventricle structure and function. *Hypertension* 2002;40:162–167.
232. Jacobi J, Hilgers KF, Schlaich MP, Siffert W, Schmieder RE. 825T allele of the G-protein beta3 subunit gene (GNB3) is associated with impaired left ventricular diastolic filling in essential hypertension. *J Hypertens* 1999;17:1457–1462.
233. Turner ST, Boerwinkle E. Genetics of blood pressure, hypertensive complications, and antihypertensive drug responses. *Pharmacogenomics* 2003;4:53–65.
234. Bray MS, Krushkal J, Li L, Ferrell R, Kardia S, Sing CF et al. Positional genomic analysis identifies the beta-adrenergic receptor gene as a susceptibility locus for human hypertension. *Circulation* 2000;101:2877–2882.
235. Busjahn A, Li GH, Faulhaber HD, Rosenthal M, Becker A, Jeschke E et al. $\beta 2$ -adrenergic receptor gene variations, blood pressure, and heart size in normal twins. *Hypertension* 2000;35:555–560.
236. Rosmond R, Ukkola O, Chagnon M, Bouchard C, Björntorp P. Polymorphisms of the beta2-adrenergic receptor gene (ADRB2) in relation to cardiovascular risk factors in men. *J Intern Med* 2000;248:239–244.
237. Jia H, Sharma P, Hopper R, Dickerson C, Lloyd DD, Brown MJ. $\beta 2$ -adrenoceptor gene polymorphisms and blood pressure variations in East Anglian Caucasians. *J Hypertens* 2000;18:687–693.

238. Hoit BD, Suresh DP, Craft L, Walsh RA, Liggett SB. $\beta 2$ -adrenergic receptor polymorphisms at amino acid 16 differentially influence agonist-stimulated blood pressure and peripheral blood flow in normal individuals. *Am Heart J* 2000;139:537–542.
239. Bengtsson K, Melander O, Orho-Melander M, Lindblad U, Ranstam J, Rastam L et al. Polymorphism in the beta-Adrenergic Receptor Gene and Hypertension. *Circulation* 2001;104:187–190.
240. Tonolo G, Melis MG, Secci G, Atzeni MM, Angius MF, Carboni A et al. Association of Trp64Arg beta 3-adrenergic-receptor gene polymorphism with essential hypertension in the Sardinian population. *J Hypertens* 1999;17:33–38.
241. Jia H, Hingorani AD, Sharma P, Hopper R, Dickerson C, Trutwein D et al. Association of the G(s)alpha gene with essential hypertension and response to beta-blockade. *Hypertension* 1999;34:8–14.
242. Miyamoto Y, Saito Y, Kajiyama N, Yoshimura M, Shimasaki Y, Nakayama M et al. Endothelial nitric oxide synthase gene is positively associated with essential hypertension. *Hypertension* 1998;32:3–8.
243. Uza G, Vlaicu R. Sodium and calcium urinary excretion in normal and hypertensive patients. *Acta Med Iug* 1975;29:393–398.
244. Lacolley PJ, Lewis SJ, Brody MJ. Role of sympathetic nerve activity in the generation of vascular nitric oxide in urethane-anesthetized rats. *Hypertension* 1991;17:881–887.
245. Kato N, Sugiyama T, Morita H, Nabika T, Kurihara H, Yamori Y et al. Lack of evidence for association between the endothelial nitric oxide synthase gene and hypertension. *Hypertension* 1999;33:933–936.
246. Kajiyama N, Saito Y, Miyamoto Y, Yoshimura M, Nakayama M, Harada M et al. Lack of association between T-786->C mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene and essential hypertension. *Hypertens Res* 2000;23:561–565.
247. Friend LR, Morris BJ, Gaffney PT, Griffiths LR. Examination of the role of nitric oxide synthase and renal kallikrein as candidate genes for essential hypertension. *Clin Exp Pharmacol Physiol* 1996;23:564–566.
248. Hyndman ME, Parsons HG, Verma S, Bridge PJ, Edworthy S, Jones C et al. The T-786->C mutation in endothelial nitric oxide synthase is associated with hypertension. *Hypertension* 2002;39:919–922.
249. Hunt SC, Williams CS, Sharma AM, Inoue I, Williams RR, Lalouel J-M. Lack of linkage between the endothelial nitric oxide synthase gene and hypertension. *J Hum Hypertens* 1996;10:27–30.
250. Bonnaireaux A, Nadaud S, Charru A, Jeunemaitre X, Corvol P, Soubrier F. Lack of evidence for linkage of the endothelial cell nitric oxide synthase gene to essential hypertension. *Circulation* 1995;91:96–102.
251. Takami S, Wong ZY, Stebbing M, Harrap SB. Linkage analysis of endothelial nitric oxide synthase gene with human blood pressure. *J Hypertens* 1999;17:1431–1436.
252. Katori M, Majima M. The renal kallikrein-kinin system: its role as a safety valve for excess sodium intake, and its attenuation as a possible etiologic factor in salt-sensitive hypertension. *Crit Rev Clin Lab Sci* 2003;40:43–115.
253. Berge KE, Bakken A, Bohn M, Eriksson J, Berg K. Analyses of mutations in the human renal kallikrein (hKLK1) gene and their possible relevance to blood pressure regulation and risk of myocardial infarction. *Clin Genet* 1997;52:86–95.
254. Slim R, Torremocha F, Moreau T, Pizard A, Hunt SC, Vuagnat A et al. Loss-of-function polymorphism of the human kallikrein gene with reduced urinary kallikrein activity. *J Am Soc Nephrol* 2002;13:968–976.
255. Hunt SC, Hasstedt SJ, Wu LL, Williams RR. A gene-environment interaction between inferred kallikrein genotype and potassium. *Hypertension* 1993;22:161–168.
256. Wang C, Chao L, Chao J. Direct gene delivery of human tissue kallikrein reduces blood pressure in spontaneously hypertensive rats. *J Clin Invest* 1995;95:1710–1716.
257. Trabold F, Pons S, Hagege AA, Bloch-Faure M, Alhenc-Gelas F, Giudicelli JF et al. Cardiovascular phenotypes of kinin B2 receptor- and tissue kallikrein-deficient mice. *Hypertension* 2002;40:90–95.
258. Flickinger AL, Burnett JC Jr, Turner ST. Atrial natriuretic peptide and blood pressure in a population-based sample. *Mayo Clin Proc* 1995;70:932–938.
259. Rahmutula D, Nakayama T, Soma M, Takahashi Y, Kunimoto M, Uwabo J et al. Association study between the variants of the human ANP gene and essential hypertension. *Hypertens Res* 2001;24:291–294.
260. Nannipieri M, Manganiello M, Pezzatini A, De Bellis A, Seghieri G, Ferrannini E. Polymorphisms in the hANP (human atrial natriuretic peptide) gene, albuminuria, and hypertension. *Hypertension* 2001;37:1416–1422.
261. Nakayama T, Soma M, Mizutani Y, Xinjuan X, Honye Y, Kaneko Y et al. A novel missense mutation of exon 3 in the type A human natriuretic peptide receptor gene: possible association with essential hypertension. *Hypertens Res* 2002;25:395–401.
262. Nakayama T, Soma M, Takahashi Y, Rehemudula D, Kanmatsuse K, Furuya K. Functional deletion mutation of the 5'-flanking region of type A human natriuretic peptide receptor gene and its association with essential hypertension and left ventricular hypertrophy in the Japanese. *Circ Res* 2000;86:841–845.
263. Knowles JW, Erickson LM, Guy VK, Sigel CS, Wilder JC, Maeda N. Common variations in noncoding regions of the human natriuretic peptide receptor A gene have quantitative effects. *Hum Genet* 2003;112:62–70.
264. Nakayama T, Soma M, Watanabe Y, Hasimu B, Sato M, Aoi N et al. Splicing mutation of the prostacyclin synthase gene in a family associated with hypertension. *Biochem Biophys Res Commun* 2002;297:1135–1139.
265. Meissner I, Whisnant JP, Sheps SG, Schwartz GL, O'Fallon WM, Covalt JL et al. Detection and control of high blood pressure in the community: Do we need a wake-up call? *Hypertension* 1999;34:466–471.
266. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
267. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *Jama* 2003.
268. Cadman PE, O'Connor DT. Pharmacogenomics of hypertension. *Curr Opin Nephrol Hypertens* 2003;12:61–70.
269. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet* 1997;60:284–295.
270. Joint National Committee on Prevention D, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–2446.
271. Xu X, Rogus JJ, Terwedow HA, Yang J, Wang Z, Chen C et al. An extreme-sib-pair genome scan for genes regulating blood pressure. *Am J Hum Genet* 1999;64:1694–1701.
272. Rice T, Rankinen T, Province MA, Chagnon YC, Perusse L, Borecki IB et al. Genome-wide linkage analysis of systolic and diastolic blood pressure: the Quebec Family Study. *Circulation* 2000;102:1956–1963.
273. Hsueh WC, Mitchell BD, Schneider JL, Wagner MJ, Bell CJ, Nanthakumar E et al. QTL influencing blood pressure maps to the region of PPH1 on chromosome 2q31–34 in Old Order Amish. *Circulation* 2000;101:2810–2816.
274. Sharma P, Fatibene J, Ferraro F, Jia H, Monteith S, Brown C et al. A genome-wide search for susceptibility loci to human essential hypertension. *Hypertension* 2000; 35:1291–1296.
275. Perola M, Kainulainen K, Pajukanta P, Terwilliger JD, Hiekkalinna T, Ellonen P et al. Genome-wide scan of predisposing loci for increased diastolic blood pressure in Finnish siblings. *J Hypertens* 2000;18:1579–1585.
276. Zhu DL, Wang HY, Xiong MM, He X, Chu SL, Jin L et al. Linkage of hypertension to chromosome 2q14–q23 in Chinese families. *J Hypertens* 2001;19:55–61.
277. Atwood LD, Samollow PB, Hixson JE, Stern MP, MacCluer JW. Genome-wide linkage analysis of blood pressure in Mexican Americans. *Genet Epidemiol* 2001; 20:373–382.
278. Atwood LD, Samollow PB, Hixson JE, Stern MP, MacCluer JW. Genome-wide linkage analysis of pulse pressure in Mexican Americans. *Hypertension* 2001;37(Part 2):425–428.
279. Angius A, Petretto E, Maestrale GB, Forabosco P, Casu G, Piras D et al. A new essential hypertension susceptibility locus on chromosome 2p24-p25, detected by genome-wide search. *Am J Hum Genet* 2002;71:893–905.
280. Harrap SB, Wong ZY, Stebbing M, Lamantia A, Bahlo M. Blood pressure QTLs identified by genome-wide linkage analysis and dependence on associated phenotypes. *Physiol Genomics* 2002;8:99–105.
281. Rice T, Rankinen T, Chagnon YC, Province MA, Perusse L, Leon AS et al. Genome-wide linkage scan of resting blood pressure: HERITAGE Family Study. Health, Risk Factors, Exercise Training, and Genetics. *Hypertension* 2002;39:1037–1043.
282. Cooper RS, Luke A, Zhu X, Kan D, Adeyemo A, Rotimi C et al. Genome scan among Nigerians linking blood pressure to chromosomes 2, 3, and 19. *Hypertension* 2002;40:629–633.
283. Kristjansson K, Manolescu A, Kristinsson A, Hardarson T, Knudsen H, Ingason S et al. Linkage of essential hypertension to chromosome 18q. *Hypertension* 2002;39: 1044–1049.
284. Ranade K, Hinds D, Hsiung CA, Chuang LM, Chang MS, Chen YT et al. A genome scan for hypertension susceptibility loci in populations of Chinese and Japanese origins. *Am J Hypertens* 2003;16:158–162.
285. Thiel BA, Chakravarti A, Cooper RS, Luke A, Lewis S, Lynn A et al. A genome-wide linkage analysis investigating the determinants of blood pressure in whites and African Americans. *Am J Hypertens* 2003;16:151–153.
286. Rao DC, Province MA, Leppert MF, Oberman A, Heiss G, Ellison RC, et al. A genome-wide affected sibpair linkage analysis of hypertension: the HyperGEN network. *Am J Hypertens* 2003;16:148–150.
287. Kardia SL, Rozek LS, Krushkal J, Ferrell RE, Turner ST, Hutchinson R et al. Genome-wide linkage analyses for hypertension genes in two ethnically and geographically diverse populations. *Am J Hypertens* 2003;16:154–157.
288. Caulfield M, Monroe P, Pembroke J, Samani N, Dominiczak A, Brown M et al. Genome-wide mapping of human loci for essential hypertension. *Lancet* 2003;361: 2118–2123.