review

Genetics of hypertension

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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 tree[9] 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 hemorrhagic[34] 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

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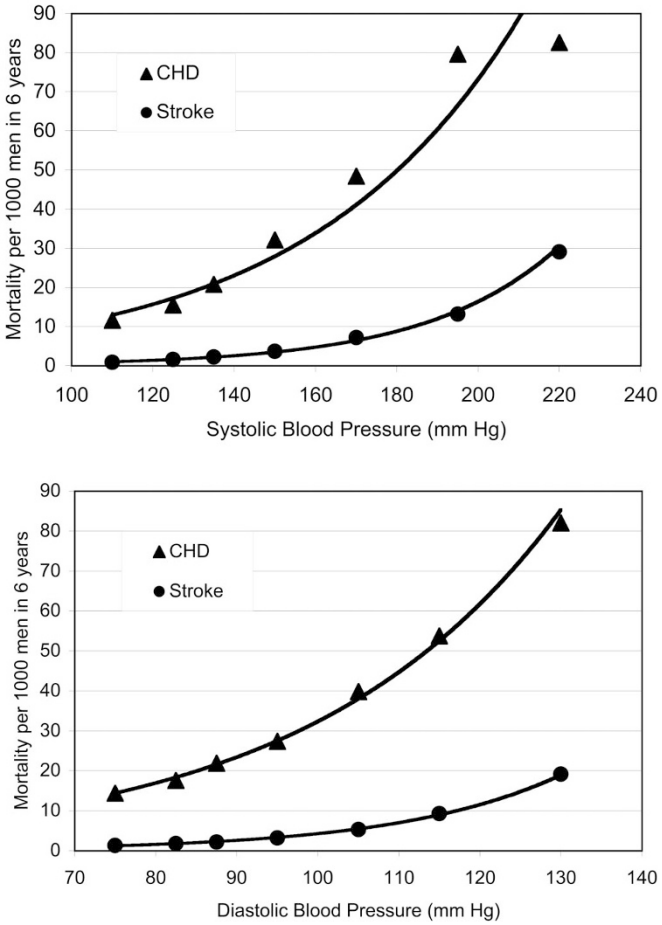

Fig. 1 Coronary heart disease (CHD) and stroke mortality in relation to systolic and diastolic blood pressure in the MRFIT study. Adapted from Neaton et al.[2]

strokes under age 65.[36] Leukoariosis 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 leukoariosis 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 mass[45] 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-

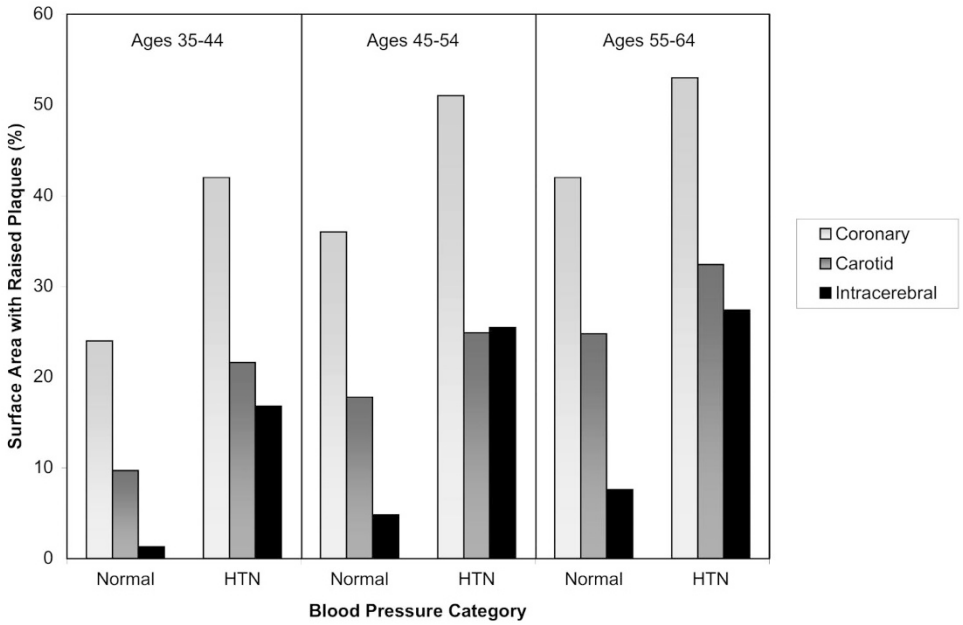

Fig. 2 Percent of surface identified with raised atherosclerotic plaques at autopsy among men from Oslo with and without diagnosed hypertension in the International Atherosclerosis Project. Adapted from Robertson et al.[3] and Solberg et al.[4]

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 Unequal fusion (chimera) of two, similar and adjacent genes, aldosterone synthase (*CYP11B2*) and 11β-hydroxylase (*CYP11B1*) due to an unequal crossing-over event (8p21)	Aldosterone synthase activity ectopically expressed in adrenal zona fasciculata due to chimeric promoter region of 11β-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.
Apparent mineralocorticoid excess Autosomal recessive Deficiency of 11β-hydroxysteroid dehydrogenase-2 (*HSD11B2, AME1,* 16q22)	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.
Steroid 11β-hydroxylase deficiency (Congenital adrenal hyperplasia IV) Autosomal recessive (*CYP11B1,* 8q21)	11β-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 17α-hydroxylase deficiency (Congenital adrenal hyperplasia V) Autosomal recessive (*CYP17,* 10q24.3)	Similar to steroid 11β-hydroxylase deficiency.
Hypertension with severe exacerbated in pregnancy Autosomal dominant MR Ser810Leu (*NR3C2*, 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 Deletions of cytoplasmic tail and some missense mutations of the epithelial sodium channel (ENaC) (*SCNN1B,* 16p13-p12)	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.
Pseudohypoaldosteronism, type II (Gordon's syndrome) (*WNK1,* 12p13) (*WNK4,* 17q21–q22) (Also linkage to 1q31–q42)	The clinical features of Gordon's syndrome include hypertension, hyperkalemia, hyperchloremia, 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 (*BBS2,* 16q21) (*BBS4,* 15q22.3–q23)	Mechanism of disease unknown.
Autosomal dominant polycystic kidney disease (*PKD1,* 16p13.3) (*PKD2,* 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	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.
Autosomal recessive	
(*CYP11B2,* 8p21)	
Congenital adrenal hyperplasia 1 steroid 21-hydroxylase deficiency	Similar to aldosterone synthase deficiency. Other endocrine abnormalities.
Autosomal recessive	
(*CYP21A2,* 6p21.3)	
Dominant Pseudohypoaldosteronism, type I	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.
Autosomal dominant	
Mineralocorticoid receptor loss of function (various mutations seen)	
(*MR,* 4q31.1)	
Recessive Pseudohypoaldosteronism, type I	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.
Autosomal recessive	Unlike dominant form, recessive does not correct with age.
(*SCNN1A,* 12p13)	
(*SCNN1B,* 16p13-p12)	
(*SCNN1G,* 16p13-p12)	
Gitelman syndrome	Impaired function of the thiazide-sensitive Na-Cl cotransporter (*SLC12A3*) 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.
Autosomal recessive	
Sodium chloride cotransporter (*SLC12A3,* 16q13)	
Bartter syndrome	Loss of function of the apical, furosemide-sensitive, Na-K-2Cl cotransporter (*SLC12A1*) 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.
Autosomal recessive	
(type 1—*SLC12A1,* 15q15-q21)	
(type 2—*ROMK* or *KCNJ1,* 11q24)	
(type 3—*CLCNKB,* 1q36)	

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*

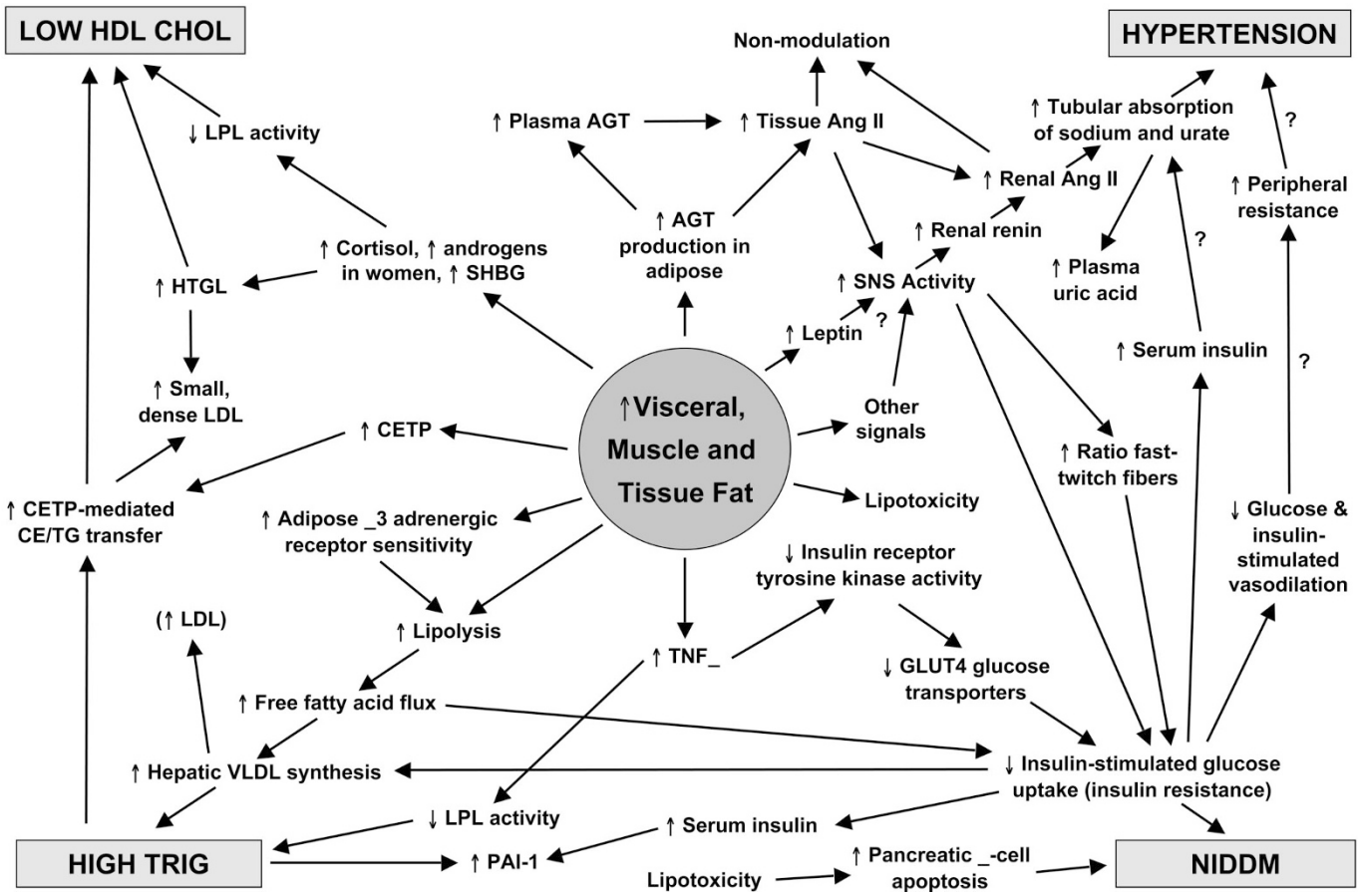

Fig. 3 Suggested pathophysiology of the metabolic syndrome.

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

			Chromosome and location (cM) of linkage																					
Ref.	Trait	Sample	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	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												
													5												
	SBP	B, F																			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
11β-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 (*NPR1*)	+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 monoxygenase 4A14 (males/females)	+30/+17
Heme oxygenase 1	+24

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 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 group[143] 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 genotype[146] 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 intake[150] have noted greater responses to the intervention in persons with the −6AA

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 women[156] 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] 11β-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 humans[175] were followed by significant linkage in hypertensive siblings[176] 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 populations.[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 of 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 diuretic[176] and greater increases in blood pressure after a saline load[159] 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 mortality[184] and left ventricle mass[185] 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 D_1 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 D_1 receptor has other intracellular effects and there are other dopamine receptors.[193] Of particular interest are observations of defective receptor coupling associated with increased D_1 receptor serine phosphorylation in both spontaneously hypertensive rats and humans with essential hypertension.[194] This increased receptor phosphorylation (resulting in uncoupling of the D_1 receptor from downstream adenylate cyclase activation) was later traced to increased activity of G protein–coupled receptor kinase 4 (*GRK4*γ).[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 *GRK4*γ variants all showing higher than normal activity.[195] Significant interaction between variants of *GRK4*γ (termed "FJ" in this study) and variants of the renin-angiotensin system was also found[158] with reportedly high prediction of hypertension status using combinations of genotypes.[196] There are reports of variants in the D_1 and D_2 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 blacks[209] 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 agonist[226] 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 β_2-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 β_1[239] and β_3-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 negative[249] 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]

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