



# Genetics of blood pressure, hypertensive complications, and antihypertensive drug responses

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Hypertension is the most prevalent, treatable risk factor for diseases of the heart, brain and kidneys. In this review, we discuss advances in understanding of the genetics of blood pressure regulation, the development of hypertensive complications and the pharmacodynamics of antihypertensive drug responses. Discovery of single gene mutations that cause hypertension or hypotension in humans suggests that the common final pathway for regulation of blood pressure level is via alterations in renal sodium handling. Based on a working hypothesis that common genetic variations contributing to blood pressure variation in the population may also act on this same pathway, we summarize supporting evidence emerging from linkage and selected association studies of candidate genes – including those encoding components of the renin-angiotensin-aldosterone system, the epithelial sodium channel, adrenoreceptors, G protein subunits, and other cellular signaling mediators and modifiers. We proceed to distinguish ischemic target organ complications due to arteriolosclerotic changes of the microvasculature from those due to atherosclerosis involving larger conduit and capacitance arteries. Using the example of subcortical white matter ischemia of the brain, we propose that interindividual variation in the arteriolosclerotic complications is more likely than atherosclerotic complications to be related to the same genetic (and environmental) mechanisms that contribute to hypertension. We conclude by summarizing the state-of-the-art of antihypertensive pharmacogenetics, which has succeeded in rejecting the null hypothesis that genetic variation does not influence blood pressure or protective target organ responses to drug therapy. In each of the three areas covered in this review, we indicate the many remaining obstacles to the routine clinical use of genetic measurements in the diagnosis, evaluation and treatment of hypertension.

## Introduction

Common diseases that have heterogeneous, multifactorial etiologies account for most morbidity, mortality and costs of healthcare. The recently completed draft sequencing of the human genome has focused attention on the potential for genetic information to benefit the diagnosis, evaluation and treatment of such common diseases. This article addresses three rapidly evolving frontiers of clinical research that have the potential to reshape approaches to the diagnosis, evaluation and treatment of high blood pressure or hypertension – one of the most common human disorders. Progress includes insights into the pathways of genetic regulation of blood pressure, the role of genetics in the pathophysiology of hypertensive target organ complications and emerging evidence of genetic influences on antihypertensive drug responses. In each area, our objective is to review current knowledge and discuss limitations to clinical application of

genotypic information in the diagnosis, evaluation and treatment of hypertension.

Blood pressure regulation and hypertension  
All hypertension can be viewed as a consequence of over filling of the arterial vascular bed with excess fluid relative to its capacity. Consequently, it is not surprising that an extensive body of evidence establishes the pre-eminent role of the kidneys' capacity for sodium excretion as the dominant long-term regulator of blood pressure level [1]. This follows from the direct positive relationship between the level of arterial pressure perfusing the kidneys and their output of sodium and water [2]. Although many other regulatory mechanisms influence blood pressure acutely, the renal mechanism of pressure-natriuresis, by controlling body fluid volume, determines the chronic steady-state level of blood pressure. Moreover, changes in tubular reabsorption of sodium, rather than filtration, are the

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common final pathway for changes in the renal 'set point' for arterial pressure.

#### *Rare single gene disorders*

Discovery of numerous single gene mutations that cause hypertension or hypotension in humans (Figure 1) supports the view that the common final pathway for regulation of blood pressure level is via alterations in renal tubular reabsorption of filtered sodium [3]. Gain-of-function mutations that increase sodium reabsorption and cause hypertension include mutations in the genes encoding the mineralocorticoid receptor (e.g., hypertension exacerbated by pregnancy), aldosterone synthase (e.g., glucocorticoid-remediable aldosteronism), other enzymes synthesizing steroids that activate the mineralocorticoid receptor (e.g., 11 $\beta$ -hydroxysteroid dehydrogenase, 17 $\alpha$ -hydroxylase and 11 $\beta$ -hydroxylase), the  $\beta$ - and  $\gamma$ -subunits of the renal epithelial sodium channel (e.g., Liddle's syndrome) and the WNK kinases (e.g., WNK1 and WNK4 in pseudohypoaldosteronism Type II). Loss-of-function mutations that impair renal sodium reabsorption and cause hypotension include genes encoding the mineralocorticoid receptor (e.g., autosomal dominant pseudohypoaldosteronism Type 1), aldosterone synthase, 21-hydroxylase, the  $\alpha$ - and  $\beta$ -subunits of the epithelial sodium channel (e.g., recessive pseudohypoaldosteronism Type 1), the thiazide-sensitive sodium chloride cotransporter (e.g., Gittelmann's syndrome), the furosemide-sensitive renal sodium-potassium-chloride cotransporter (e.g., Bartter's syndrome Type 1), the ATP-sensitive potassium channel *ROMK* (e.g., Bartter's syndrome Type 2) and chloride channel *CLCNKB* (e.g., Bartter's syndrome Type 3). Different mutations, often in the same gene, may cause hypertension or hypotension; however, common to all of these disorders is alteration of renal tubular reabsorption of filtered sodium, either directly by altered transport proteins located at luminal surface of tubular epithelial cells or indirectly by altered mineralocorticoid activity.

While accounting for only a small percentage of blood pressure variation in the population, such rare mutations are still relevant because of the insights they provide into biochemical, physiological and anatomical pathways through which common genetic variations may influence blood pressure. The striking consistency of renal tubular sodium reabsorption as the common final pathway justifies a working hypothesis that more common genetic variations may also do so

by acting through this same pathway. Below we present evidence in support of this hypothesis, which relates the previously-discussed single gene disorders of blood pressure to results of candidate gene studies and genome-wide linkage studies of more common forms of hypertension.

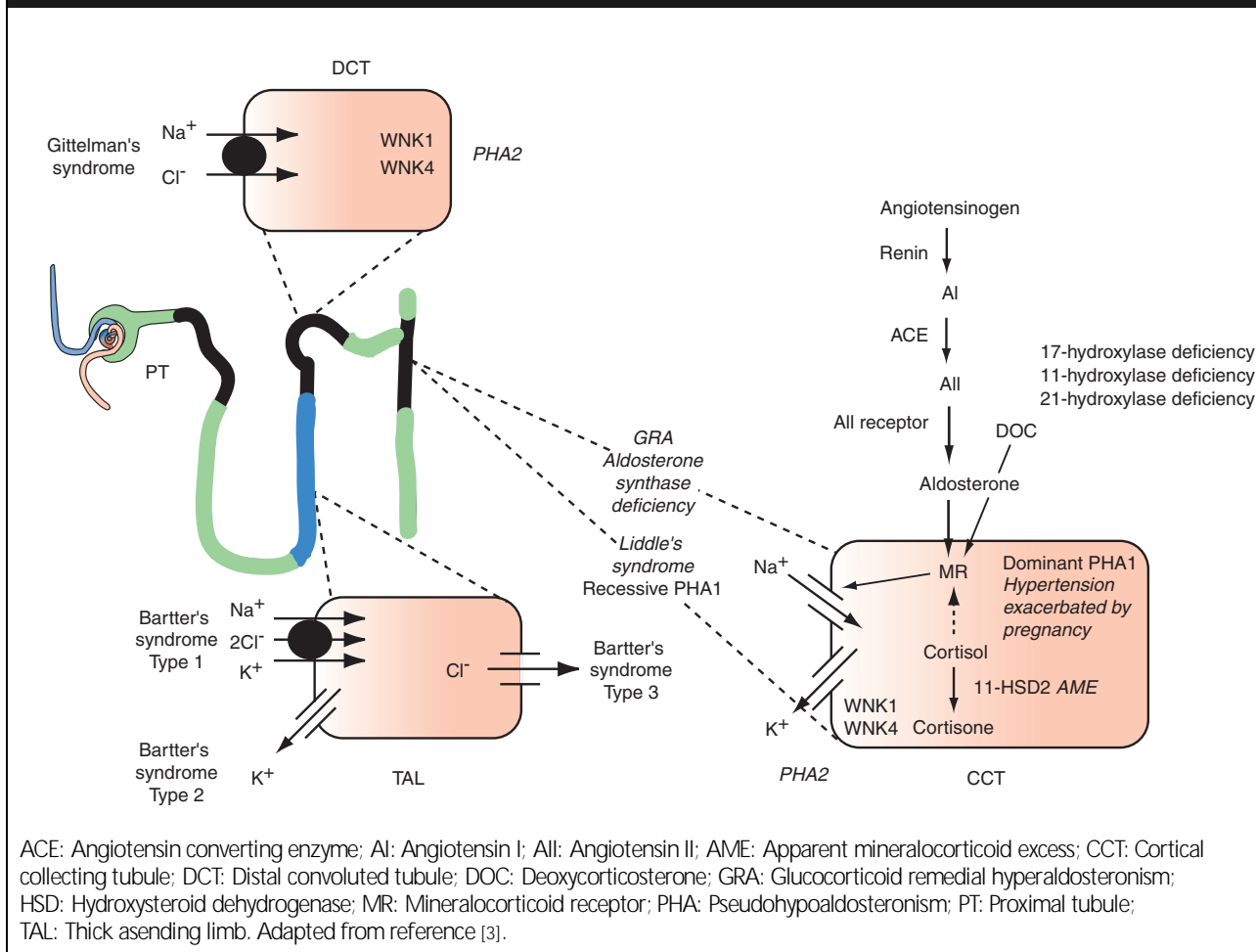
#### *Candidate gene studies*

No single genetic variant has emerged from linkage or association analyses as consistently related to blood pressure level or diagnostic category (i.e., hypertension versus normotension) in every sample and in all populations. However, polymorphisms in candidate genes encoding proteins known to influence renal tubular sodium transport, either directly or indirectly through effects on intrarenal hemodynamics, have been associated with differences in blood pressure level or diagnostic category in many of these studies. Prominent have been polymorphisms in genes of the renin-angiotensin-aldosterone system – in particular, angiotensinogen [4], angiotensin converting enzyme (ACE) [5], the angiotensin II receptor (Type 1) [6] and aldosterone synthase [7]. The end product of the renin-angiotensin cascade, angiotensin II, may enhance renal tubular sodium reabsorption both directly and indirectly via stimulation of aldosterone synthesis and release. Polymorphisms in two of these genes, angiotensinogen and ACE, have been associated with functional differences in the encoded gene products [4,8] and with measures of 'sodium sensitivity,' as measured by blood pressure response to changes in sodium intake [9].

Functional polymorphisms of the genes encoding subunits of the epithelial sodium channel may also influence renal sodium reabsorption directly and have been associated with hypertension, particularly among blacks of African descent [10], among whom sodium sensitivity is frequently reported. A polymorphism in the  $\beta$ 3-subunit of pertussis toxin sensitive G proteins, which has been associated with a shortened variant of the G $\beta$ 3 protein [11], was originally identified in lymphocytes from hypertensive individuals with increased sodium-proton antiport activity in response to agonists [12]. Among hypertensive subjects, this polymorphism has also been associated with obesity, low plasma renin, and sodium sensitivity [13,14].

Polymorphisms in the gene encoding the  $\beta$ <sub>2</sub>-adrenergic receptor are also among those frequently associated with blood pressure and essential hypertension [15]. In addition to influencing arterial dilatory responses to agonists,

**Figure 1. Single gene disorders causing hypertension (italicized) or hypotension in humans by influencing renal sodium handling.**



$\beta_2$ -adrenergic receptors appear to be present in both the proximal tubule and the distal convoluted tubule [16].  $\beta_2$ -adrenergic receptors may also influence tubular sodium reabsorption through regulation of the sodium-potassium ATPase pump in the basolateral membrane, which in turn may lead to increased sodium-proton exchange at the apical membrane [17].

Finally, single nucleotide polymorphisms (SNPs) in the gene encoding  $\alpha$ -adducin have been associated both with essential hypertension and with altered pressure-natriuresis and enhanced antihypertensive response to diuretic therapy [18,19].  $\alpha$ -Adducin forms half of a heterodimeric cytoskeletal protein ( $\alpha/\beta$  adducin) that is thought to anchor and regulate activity of the sodium-potassium ATPase pump. There are likely many other genes that influence blood pressure via direct and indirect effects on renal tubular sodium reabsorption. Since the effects of variation in most single genes on blood pressure

level are small, inconsistency of findings among association or linkage studies is not surprising. Even so, a systematic and comprehensive examination of sequence variations within such candidate genes can contribute to greater understanding of the mechanisms controlling blood pressure and the pathways through which variation in these genes influences diagnostic category in the general population.

#### Genome-wide linkage analyses

Many of the genes responsible for rare Mendelian forms of hypertension were first localized by genome-wide linkage analyses. We completed the first genome-wide linkage analyses to localize genes influencing blood pressure level in a sample from the Rochester MN population [20]. Subsequently, other studies have been published reporting regions harboring genes influencing blood pressure level or diagnostic category [21-33] (Table 1). Although multiple

**Table 1. Genomewide scans reporting evidence of linkage.**

Ref.	Trait	Chromosomes with ≥ 1 regions harboring genes influencing blood pressure																	Sample						
[20]	SBP	2	5	6															15	W	S				
[21]	SBP	2	3	4	7				11										16	17	20	C	S		
	DBP				7			10	12												20	21			
[22]	SBP			5															15	17		W	F		
	DBP																				17	18			
[23]	SBP	1	2	3	5	7	8	10	12	14											19	22	W	F	
[24]	SBP	2																					W	F	
	DBP	2																							
[25]	HTN								11														W	S	
[26]	DBP	1	2	3																		22	X	W	S
[27]	HTN	2																					C	S	
[28]	SBP																				18	21	W	F	
	DBP	2			8																				
[29]	PP				7	8															18	21			
[30]	SBP	1	2		7																		W	F	
	DBP	2																							
	MAP	1	2	4	7																				
[31]	HTN	1			7																15		W	F	
	SBP				6																				
[32]	HTN	1	2							13	15	17	19										W	F	
[33]	SBP	2	3	4	6	7	9	11													19		B	F	
	DBP	1	2	3	5	7	8	10													19				
Positive studies*		6	8	4	4	4	3	6	3	1	3	3	3	1	1	4	1	3	2	3	1	2	2	1	

\*Number of positive studies includes only studies conducted in independent samples.  
 B: Blacks; C: Chinese; DBP: Diastolic blood pressure; F: Families; HTN: Hypertension; MAP: Mean arterial pressure; S: Sibling pairs; SBP: Systolic blood pressure; W: Whites.

chromosomal regions were identified in each study – for example, four regions on chromosomes 2, 5, 6 and 15 (see Table 1) were identified in our Rochester sample [20] – three regions in particular warrant further discussion.

One region identified by Krushkal *et al.*, 5q33-5q35, contains genes encoding the  $\beta_2$ -adrenergic receptor, the  $\alpha_{1b}$ -adrenergic receptor and the dopamine receptor [34]. We resequenced each of these genes to identify the extent of DNA sequence variations in the population sampled and conducted a series of association studies to identify which positional candidate variants may be responsible for our linkage findings [15]. The results indicated that the Arg16→Gly and Gln27→Glu polymorphisms in the  $\beta_2$ -adrenergic receptor gene (*ADRB2*) influence blood pressure levels and diagnostic category in the Rochester MN population. As mentioned above, polymorphic variation in the  $\beta_2$ -adrenergic

receptor may modulate arterial tone and renal sodium reabsorption in response to  $\beta_2$ -adrenergic stimulation. In addition, the Arg16→Gly and Gln27→Glu substitutions have been shown to alter  $\beta_2$ -adrenergic receptor function *in vitro* [35].

A second linked region on human chromosome 17 [22] is of interest because it colocalizes with a region containing two recently-discovered genes responsible for pseudohypoaldosteronism Type II, the *WNK1* and *WNK4* genes [36]. Both genes encode members of the WNK family of serine-threonine kinases, components of a signaling pathway not previously implicated in the regulation of blood pressure. It is relevant to assess whether common variations in *WNK1* and *WNK4*, which are likely to have much smaller effects, are influencing net renal sodium reabsorption and contributing to differences in a blood pressure level and diagnostic category in the population-at-large. Together these studies

**Table 2. Ischemic target organ complications in hypertension.**

Target organ	Disease process	
	<i>Atherosclerosis</i>	<i>Arteriolosclerosis</i>
Brain	Cortical infarction	Lacunar infarction Leukoaraiosis
Heart	Myocardial infarction	Microvascular angina Diastolic heart failure?
Kidney	Renal artery stenosis	Albuminuria Nephrosclerosis

emphasize the potential of genome scanning studies to discover novel genes and pathways involved in the regulation of blood pressure that may become targets for the development of new antihypertensive drugs [36].

A third linked region on human chromosome 2 merits exploration because of the consistency among results of linkage studies [20,23,24,26-28,30,32,33]. Like the other implicated regions, those on chromosomes 2 appear to contain multiple candidate genes influencing blood pressure, including genes encoding ion transporters, G-protein-coupled adrenergic receptors and membrane skeletal proteins. However, encouraging the positive results from these early genome-wide linkage scans may appear, they represent only a first step toward identification of the responsible gene(s) and their DNA sequence variation(s).

#### Genetic susceptibility to target organ damage

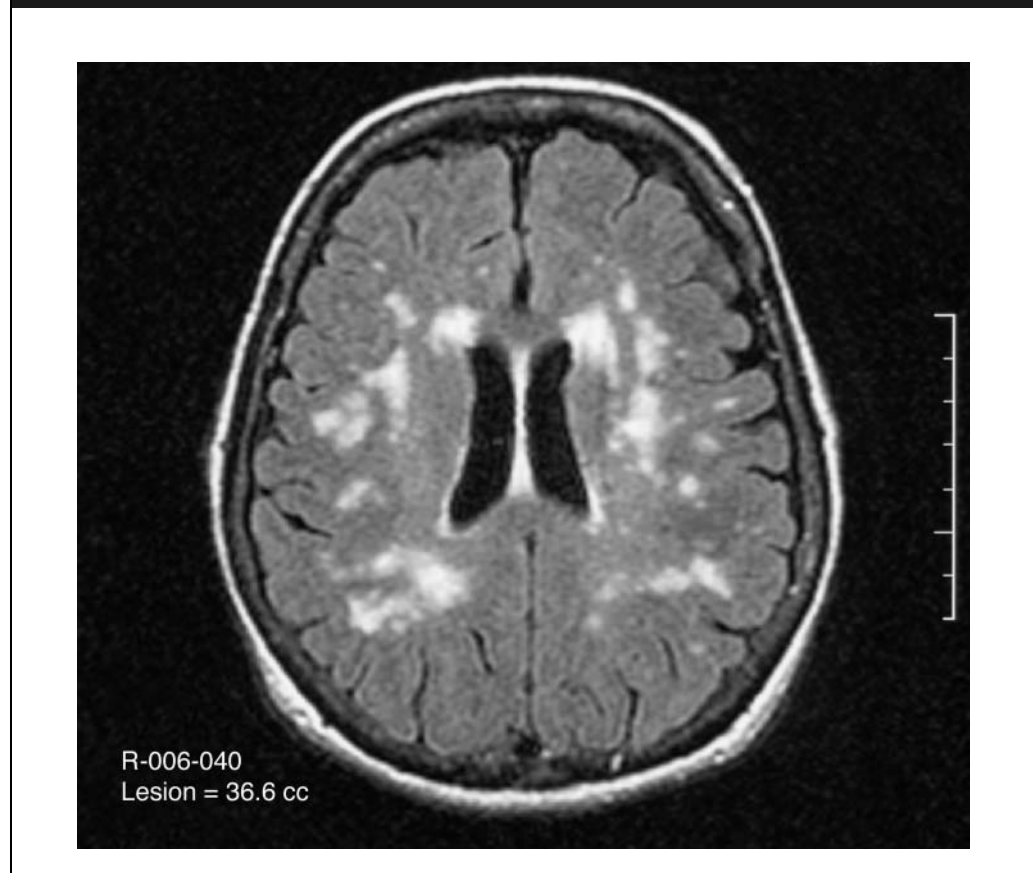
The potential for interindividual differences in the etiologic factors and pathogenetic mechanisms of hypertension to also give rise to variation in the development of target organ complications is emphasized by the observation that many vasoconstrictor, antinatriuretic and neuroexcitatory substances (e.g., angiotensin II, norepinephrine and endothelin) not only raise blood pressure but also stimulate cellular growth and vascular remodeling – two recognized features of both the macro- and microvascular complications of hypertension. Moreover, several characteristic features of the remodeling in small resistance arteries and arterioles of hypertensive individuals and in their young normotensive offspring appear to be related not only to the initial development and maintenance of elevated blood pressure but also to the subsequent development of arteriolosclerotic complications with aging [37]. As a consequence of arteriolar rarefaction, tortuosity and luminal narrowing due to medial

thickening, vasodilatory reserve becomes limited and the capacity for autoregulation of flow is shifted to a higher, narrower range of pressures [38]. Thereby, target organs – chiefly, the brain, heart and kidneys – become susceptible to blood pressure that is too low as well as blood pressure that is too high, even in the absence of atherosclerotic obstructions of larger, upstream conduit arteries. The manifestations of ischemic damage to each of these organs appear in two more or less distinct forms – those caused by atherosclerotic disease of the large elastic and medium-sized arteries delivering blood to the organ and those primarily caused by arteriolosclerotic disease of the small arteries and arterioles within the organ itself (Table 2). Atherosclerosis primarily involves remodeling of the intimal layer of the vessel wall, whereas arteriolosclerosis is distinguished by remodeling of the medial layer. A further clinically relevant distinction between ischemic manifestations of arteriolosclerosis versus atherosclerosis is that mortality related to the atherosclerotic complications appears to be declining, while the prevalence and incidence of complications related to arteriolosclerosis appear to be on the rise [39].

#### *Biometrical genetic studies*

Accurate non-invasive methods to detect and quantitate microvascular disease involving the heart and kidneys have not yet been applied in large population or family-based samples [40]. However, magnetic resonance imaging (MRI) of the brain provides such a method of detecting ischemic changes leading to incomplete infarction of the subcortical white matter supplied by penetrating end arterioles [41]. Age and hypertension are the two most consistently identified risk factors for such lesions [42-44], which appear as foci of increased T-2 signal (i.e., hyperintensity) on MRI and are referred to as leukoaraiosis (Figure 2). Leukoaraiosis, which denotes diminished intensity of the

Figure 2. Ischemic damage to the subcortical white matter, referred to as leukoaraiosis, appears as areas of increased T-2 signal on MR imaging.



medium used to image the subcortical white matter, reflects the loss of myelin and increased water content in ischemic areas of gliosis. Although most leukoaraiosis is subclinical, its functional consequence and clinical relevance derives from the association of large volumes of leukoaraiosis with impaired cognitive function, disturbed gait and disordered mood [42].

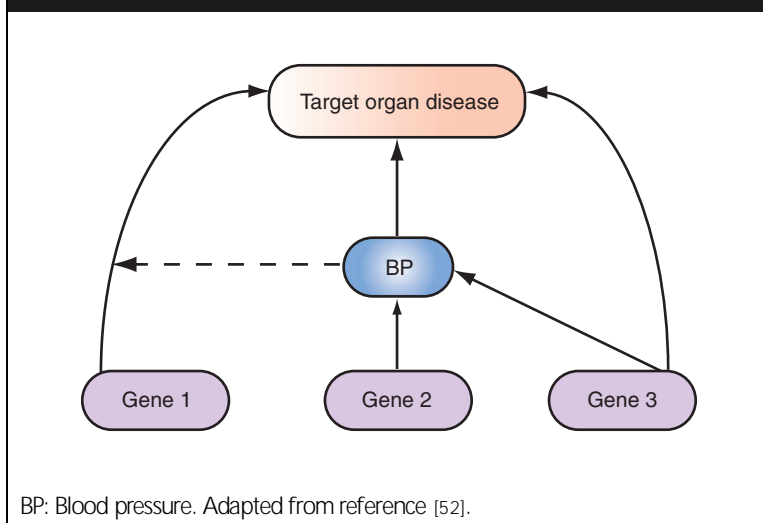
Strong evidence for genetic variance in MRI measures of leukoaraiosis was recently provided by a study of normal elderly male twins [45]. Brain MRI scans (1.5T) were obtained from 74 monozygotic (MZ) and 71 dizygotic (DZ) white male twins, ages 68–79 when scanned. Genetic modeling estimated the heritability of leukoaraiosis volume to be 73%; correction for age and head size reduced the heritability to 71% (95% confidence interval, 66–76%). Proband concordance rates for large volumes of leukoaraiosis (i.e., > 10 cm<sup>3</sup>) were 61% in MZ twins and 38% in DZ twins, compared with a prevalence of 15% in the entire sample. Moreover concordance rates for hypertension and stroke observed in the sample were much lower than for large

volumes of leukoaraiosis, suggesting that genetic factors influencing risk factors are unlikely to account for all of the genetic influence on the volume of leukoaraiosis.

#### *Candidate genes studies*

Despite considerable literature supporting a genetic contribution to atherosclerotic manifestations of hypertensive disease, few studies have attempted to identify genes contributing to its arteriosclerotic complications (Table 1). Most candidate gene studies of leukoaraiosis, for example, have involved genes encoding components of the renin-angiotensin-aldosterone system. The T235 allele of the gene encoding angiotensinogen and the deletion (D) allele of the gene encoding ACE were found to be associated with leukoaraiosis [46,47]. Other reported associations with leukoaraiosis have included polymorphisms in the genes coding for apolipoprotein E [48], apolipoprotein(a) and methylenetetrahydrofolate reductase [49] and paraoxanase 1 [50]. Intriguingly, mutations in the human Notch 3 gene on chromosome 19p13 have been

**Figure 3. Genetic pathways hypothesized to contribute to hypertension-associated target organ disease by influencing blood pressure levels or through blood pressure-independent pathways.**



identified to account for the rare mendelian disorder of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [51]. Although hypertension is not a feature of the disorder, it is characterized by small vessel and neuropathic changes reminiscent of those underlying leukoaraiosis.

Research studies are just beginning to identify genes that contribute to the microvascular complications of hypertension and to characterize whether the effects of these genes are mediated through measures of blood pressure or via mechanisms other than blood pressure. A working hypothesis regarding genes contributing to development of hypertension-related target organ diseases is illustrated in Figure 3. First, there may be genes that do not directly influence blood pressure but that cause primary disease of a target organ (gene 1). Elevated blood pressure, if present for other reasons, may simply aggravate or accelerate the effect of such genes on the primary disease process (interrupted arrow in Figure 3). Second, there may be genes that directly influence blood pressure and elevated blood pressure may in turn directly contribute to the development of target organ disease (gene 2). Third, there may be genes that contribute to target organ damage both through effects on blood pressure and via pathways separate from blood pressure (gene 3).

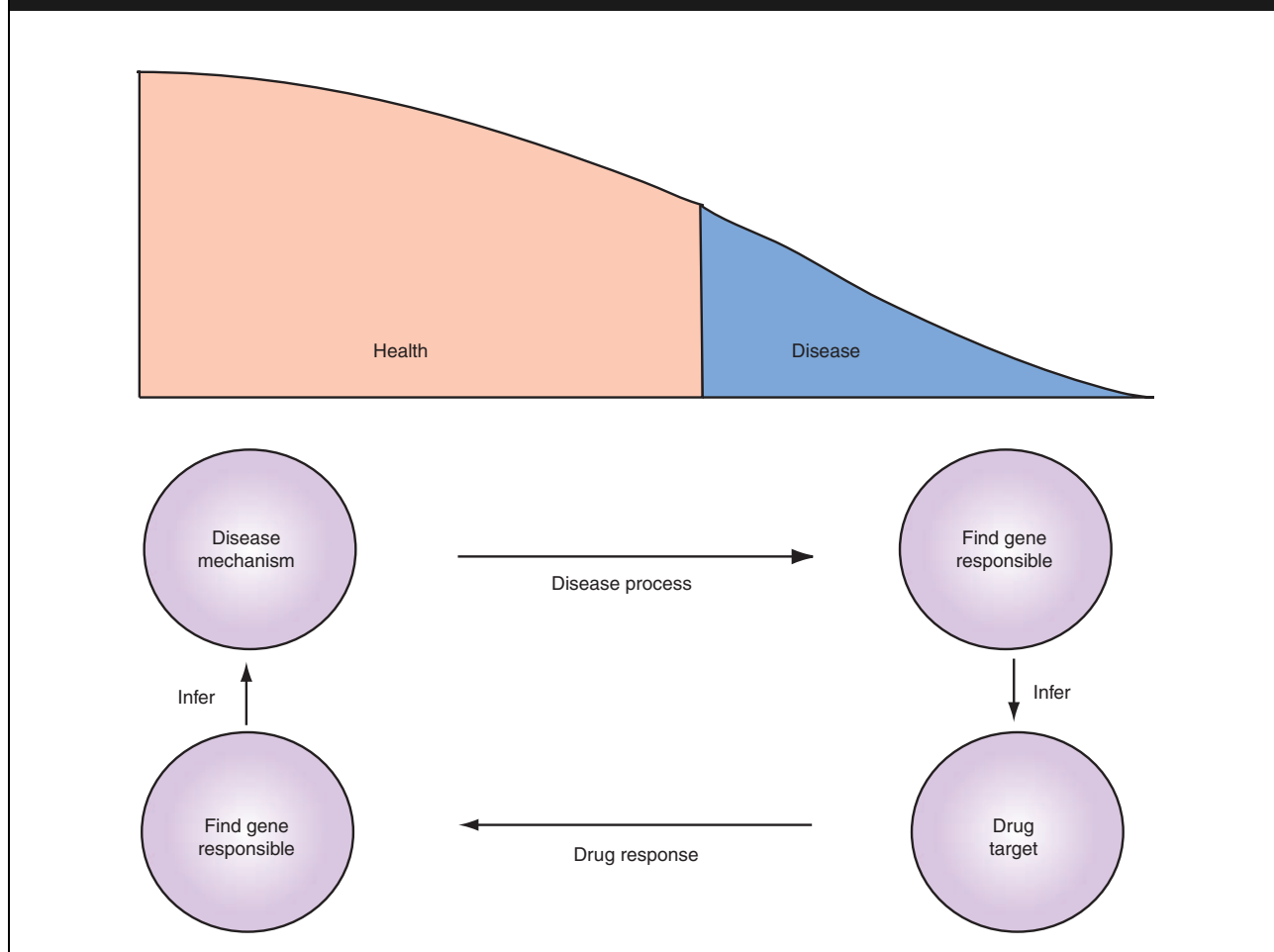
#### Antihypertensive pharmacogenetics

Although it has long been recognized that the efficacy and side effects of medications are influenced by genetic factors, pharmacogenetic discoveries have been mostly limited to polymorphisms of drug metabolizing enzymes. Only a few  $\beta$ -blockers metabolized by the polymorphic cytochrome P450 enzyme CYP2D6 are still in common use [52]. In contrast to pharmacokinetic mechanisms, pharmacodynamic mechanisms govern the interaction of the drug with its receptor and the subsequent events that determine the therapeutic effect. Consequently, pharmacodynamic response mechanisms may bear close reciprocal relationships to the pathogenic mechanisms determining disease onset, severity and development of hypertensive complications (Figure 4).

Less than 40% of treated hypertensives have their blood pressures controlled [53]. For each class of antihypertensive drugs, blood pressure responses vary among patients, with standard deviations of response as large as mean responses and ranges of response several times greater than mean responses. Moreover, a sizable minority of subjects (10–20%) experiences no decrease or a paradoxical increase in blood pressure. Largely due to pharmacodynamic differences, such inter-individual variation in response reflects the variety of pathophysiological mechanisms contributing to hypertension.

There are several reasons why measurements of genetic variation may improve the prediction of antihypertensive drug responses beyond what is possible with conventional demographic and biochemical approaches to profiling. In contrast to most conventional measures, the information encoded in genes is invariant with time and most environmental exposures and can be measured more accurately than conventional biochemical and physiological traits. Genes may also contain information about regulatory activity of systems within compartments of the kidneys, heart, brain and the vasculature that are inaccessible to direct measurement and not accurately reflected in blood, urine or by other non-invasive measurements. Finally, measurement of SNPs, the most abundant form of genetic variation in human genome, is well-suited for automation and advances in large-scale genotyping technologies, coupled with those in computer hardware and software, makes the prospect of rapidly obtaining and interpreting variation measured at thousands of sites throughout the genome increasingly feasible.

Figure 4. Reciprocal relationships between hypertension genes and drug response genes. Pathogenetic mechanisms of blood pressure elevation appear to be inversely related to the pharmacodynamics of antihypertensive drug responses.



#### *Candidate gene studies*

Logical candidates genes to influence antihypertensive drug responses are those that code for components of the system targeted by a drug or of a counter regulatory system opposing the initial drug-induced fall in blood pressure. Thus, far, the largest and most carefully conducted human studies have focused on candidate gene polymorphisms predictive of antihypertensive responses to diuretics, which initially act to lower blood pressure by inhibiting renal tubular sodium reabsorption.

#### *$\alpha$ -Adducin*

Cusi and colleagues tested whether the Gly460Trp polymorphism of the gene encoding  $\alpha$ -adducin in subjects with essential hypertension was associated with differences in the blood pressure response to acute or chronic diuretic treatment with furosemide or hydrochlorothiazide, respectively [18]. In each drug

treatment protocol, the average blood pressure reduction was more than two times greater in heterozygotes carrying the Trp460 variant than in Gly460 homozygotes. These findings have been confirmed in a subsequent Italian trial [54]. They illustrate the potential to draw pathophysiologic inferences regarding the mechanisms contributing to hypertension based on predictors of response to drugs targeting known regulatory systems.

#### *$\beta$ 3 subunit of G proteins*

In a biracial sample of ~ 200 African-American and ~ 200 non-Hispanic Caucasians with previously diagnosed hypertension, we observed that the declines in blood pressure in response to hydrochlorothiazide differed significantly among C825T genotype groups of the gene encoding the  $\beta$ 3 subunit of G proteins, with the magnitude of response increasing with the number of 825T alleles [55]. When the C825T

genotype was added to regression models that included other predictors of greater blood pressure responses (i.e., higher pretreatment blood pressure levels, black race, female gender, older age, greater waist-to-hip ratio; and lower pretreatment plasma renin activity, aldosterone concentration and urinary aldosterone excretion), the genotype remained a statistically significant predictor of systolic and diastolic blood pressure responses. By itself, the C825T polymorphism accounted for < 5% of interindividual variation in blood pressure responses and the combined effects of all identified predictors accounted for only 32% of interindividual variation in systolic blood pressure response and 18% of variation and diastolic blood pressure response.

#### *Genes of the renin-angiotensin-aldosterone system*

In smaller Caucasian and Japanese samples, variation in genes of the renin-angiotensin-aldosterone system have been investigated for relationships with antihypertensive responses to ACE inhibitors,  $\beta_1$ -blockers and calcium channel blockers [56]. The findings have been inconsistent. In a recent Swedish study investigating the effects of treatment with an angiotensin II receptor blocker (versus  $\beta$ -blocker) on left ventricular mass, Kurland and colleagues reported that hypertensive individuals homozygous for the ACE I allele had significantly greater reductions in diastolic blood pressure than those carrying the D allele [57]. In contrast, polymorphisms in the genes encoding angiotensinogen (T174→M) and the angiotensin II receptor (Type 1) (A1166→C) did not influence response to treatment; however these latter polymorphisms but not a polymorphism in the gene encoding aldosterone synthase (C(-344)→T), were predictive of differences in the regression of left ventricular hypertrophy [58]. Although findings have been mixed [56], investigations of other cardiovascular responses to antihypertensive drug therapy have provided some support for the belief that activation of the renin-angiotensin-aldosterone system contributes to the development of hypertensive complications and adverse outcomes [59].

#### *Genome-wide scans*

To our knowledge, the only published genome-wide search for a pharmacogenetic trait locus employed a rodent model of genetic hypertension to identify a region on rat chromosome 2

containing a gene influencing blood pressure response to a dihydropyridine calcium channel blocker (PY108-068) [60].

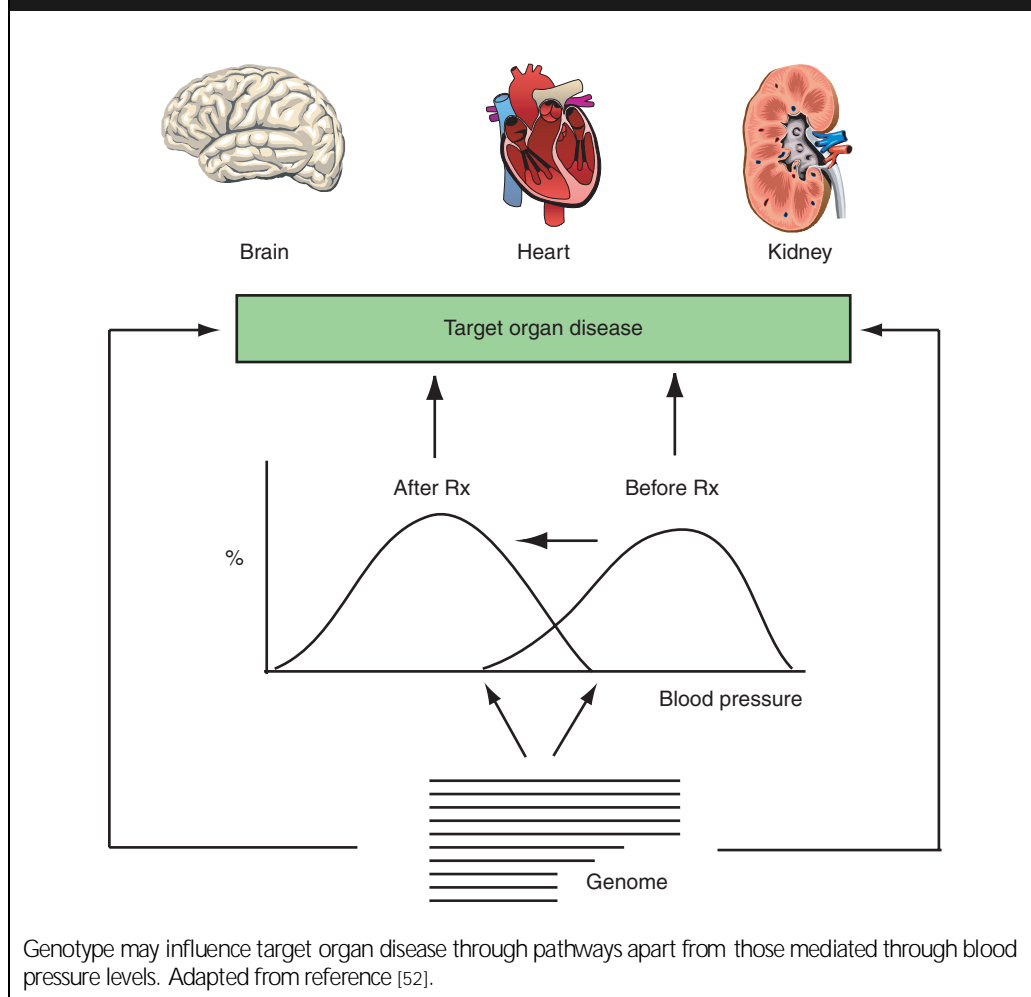
Unfortunately, the sample design and methods of genome-wide linkage studies, which typically employ highly polymorphic genetic markers measured in large numbers of biologically-related family members, are not feasible for investigation of most drug response traits in humans. In contrast, genome-wide association studies can be conducted in unrelated hypertensive individuals, the traditional sample design of large-scale antihypertensive drug trials. Moreover, association studies contrasting allele and haplotype frequencies between individuals selected from opposite extremes of the drug response distribution are inherently more powerful than linkage studies to identify quantitative trait loci with small effects on drug response [61]. Development of dense maps of SNPs and the technologies to rapidly and accurately genotype samples at thousands of loci throughout the genome promise to also fulfil the needs to consider the combined and interacting effects of variation at many loci.

#### *Prevention of target organ complications*

The ultimate objective of antihypertensive drug therapy is to prevent the development of adverse clinical outcomes resulting from target organ damage. Blood pressure levels measured before or after initiation of drug therapy can account for only a small portion of the total variation in susceptibility to develop target organ complications from hypertension. Much of the remaining, unexplained variation appears to have a genetic basis (Figure 5). Emerging evidence of differences in cardiovascular disease outcomes among patients randomized to receive antihypertensive drugs with different pharmacodynamic mechanisms of action also suggests that genetic make-up – apart from its effects on blood pressure response to antihypertensive therapy – influences the protective effects of these therapeutic agents. Two studies have already demonstrated that candidate gene polymorphisms are associated with differences in clinical cardiovascular disease end points among treated hypertensive patients [62,63].

The first study involved patients treated with  $\beta$ -blockers for heart failure, a common sequel of hypertension [62]. In 328 patients with left heart failure (ejection fraction  $\leq 0.45$ ), transplant-free survival was predicted by the insertion/deletion polymorphism in the gene encoding ACE and

**Figure 5. Genotype dependence of protective effects of antihypertensive drug therapy.**



was significantly worse in those with the deletion allele. This difference was seen in the whole cohort and among patients not treated with  $\beta$ -blockers but not among those treated with  $\beta$ -blockers. Thus, despite the treatment of most of these patients with ACE inhibitors or angiotensin II receptor blockers, the effectiveness of  $\beta$ -blockers to enhance transplant-free survival depended upon the ACE genotype.

In another study, Psaty and colleagues demonstrated that diuretic antihypertensive therapy was associated with significantly lower risk of myocardial infarction and stroke in carriers of the  $\alpha$ -adducin variant Gly460 $\rightarrow$ Trp [63]. In contrast, the protective effects of other antihypertensive therapies were not dependent on  $\alpha$ -adducin genotype. Among 385 carriers of the adducin variant allele, diuretic therapy was associated with a 45% lower risk of myocardial infarction and stroke outcomes – a relationship that was

not observed for other antihypertensive drug therapies. This genotype-by-drug interaction was independent of age, sex, race, diabetes and history of cardiovascular disease. The  $\alpha$ -adducin genotype was not associated with differences in blood pressure level. Although the mechanisms responsible for the genotype-by-drug interactions observed in this and the previous study remain uncertain, the findings illustrate the potential to use genetic information to match drug therapy to the pathophysiologic disturbances in individual patients, thereby enhancing overall effectiveness by tailoring different pharmacological interventions to the particular subgroups most likely to benefit.

#### Expert opinion and outlook

It is axiomatic that interindividual variation in medically important human traits arises from the combination of genetic and environmental varia-

## Highlights

- Hypertension is the most prevalent, treatable risk factor for diseases of the heart, brain, and kidneys.
- Discovery of single gene mutations that cause hypertension or hypotension in humans suggests that the common final pathway for regulation of blood pressure level is via alterations in renal sodium handling.
- Antihypertensive pharmacogenetics has succeeded in rejecting the null hypothesis that genetic variation does not influence blood pressure or protective target organ responses to drug therapy.
- With complete sequencing of the human genome, locations of all the responsible genes have been identified, including those contributing to the development of hypertension, its target organ complications and to differences in antihypertensive drug responses.

tion. With complete sequencing of the human genome, locations of all the responsible genes have been identified, including those contributing to the development of hypertension, its target organ complications and to differences in antihypertensive drug responses. The remaining challenge is to ascertain which of the newly-discovered genes influence blood pressure, assess the extent and impact of their polymorphisms and distinguish which pathways are valid tar-

gets for intervention. Elucidation of the genetic basis of hypertension and its complications is a reciprocal process to the discovery of genes influencing antihypertensive drug responses: disease genes become candidates to influence response to therapeutic interventions and drug response genes become candidates to influence disease activity (Figure 4). Both processes facilitate the development of novel preventive and diagnostic approaches that are based on a deeper understanding of the molecular determinants of the disease in individual patients. Consequently, the collection and analyses of large amounts of genetic information in the coming years has the potential to revolutionize the approaches to the prevention, evaluation and treatment of hypertension and its associated target organ diseases.

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