Antihypertensive pharmacogenetics: getting the right drug into the right patient
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Pharmacogenetic investigation seeks to identify genetic factors that contribute to interpatient and interdrug variation in responses to antihypertensive drug therapy. Classical studies have characterized single gene polymorphisms of drug metabolizing enzymes that are responsible for large interindividual differences in pharmacokinetic responses to several antihypertensive drugs. Progress is being made using candidate gene and genome scanning approaches to identify and characterize many additional genes influencing pharmacodynamic mechanisms that contribute to interindividual differences in responses to antihypertensive drug therapy. Knowledge of polymorphic variation in these genes will help to predict individual patients' blood pressure responses to antihypertensive drug therapy and may also provide new insights into molecular mechanisms responsible for elevation of blood pressure. \textit{J Hypertens} 19:1–11 © 2001 Lippincott Williams & Wilkins.

Introduction

It has long been suspected that interindividual variation in the efficacy and side-effects of medications may be influenced by genetic factors [1]. Pharmacogenetics, defined as ‘the study of the role of genetics in drug response’ [2], is based on the tenet that ‘the genetic endowment of the individual, phenotypically expressed in protein structure, configuration and concentration, may alter drug action in multiple ways’ [3]. Until recently, the only pharmacogenetic phenomena known to influence blood pressure response to antihypertensive therapy were single gene polymorphisms with large effects on the metabolism of a few drugs that are no longer widely used. Genes coding for the enzyme variants determining these discretely distributed differences in drug disposition have been identified, and the responsible mutations within these genes are well characterized. With the mapping and sequencing of all human genes soon to be completed [4], attention is turning to identification and characterization of genes with more modest effects on drug action that contribute to continuously distributed variation in blood pressure responses to the antihypertensive medications now in common use. Identification of these genes is being accelerated by technological advances that facilitate measurement of DNA sequence variation throughout the genome and by the discovery of genes contributing to interindividual differences in blood pressure level and the occurrence of hypertension [5–8]. Knowledge of genes that influence the pharmacodynamic determinants of blood pressure response to antihypertensive medications has the potential to provide new insights not only into molecular mechanisms influencing drug response, but also into the role that these genes may play in determining interindividual differences in blood pressure level and the occurrence of hypertension.

The objectives of this review are (i) to present pharmacogenetic concepts relevant to antihypertensive drug therapy; (ii) to consider the challenge of identifying individual genetic factors that contribute to differences in responses to antihypertensive medications; (iii) to describe classical pharmacogenetic investigations successful in identifying single gene polymorphisms with large effects on the metabolism of several antihypertensive drugs; (iv) to provide examples of candidate gene and genome scanning approaches now being applied to identify genes contributing to continuously distributed variation in blood pressure response to antihypertensive medications; and (v) to suggest developments likely in the future to expand the role of pharmacogenetics in the evaluation, treatment, and control of hypertension and its complications.

Basic concepts

A variety of mechanisms determine drug response (Fig. 1). Pharmacokinetic mechanisms that determine the level of the drug in the blood, and ultimately at its
target, include absorption of the drug, its distribution, excretion and metabolism. These mechanisms that determine the fate of the drug itself are distinguished from pharmacodynamic mechanisms that govern the interaction of the drug with its target and the subsequent cellular and systemic events that occur as a consequence of this interaction. Genetic variation that alters the structure, configuration or quantity of any of the proteins involved in any of these mechanisms may contribute to interindividual variation in drug response.

When a standard dose of a drug is given to a group of individuals and an index of response is measured and plotted, several types of frequency distribution curves can be observed. Rarely, the distribution of responses is bimodal (Fig. 2). Separate subpopulations with distinctly different drug responses suggest that a single factor, possibly segregation of alleles at a single genetic locus, has a large effect on drug response [9]. In contrast, for most drugs, the frequency distribution histogram for most measures of response is unimodal and bell-shaped, or a so-called ‘normal’ or Gaussian distribution (Fig. 2). Such a frequency distribution is consistent with multifactorial determination by effects of many genetic and environmental factors, with no single factor having a discernibly large effect on response. Clearly, when the distribution of responses is continuous and unimodal, it is more difficult to identify the effects of individual genes.

**The challenge: heterogeneity of hypertension and antihypertensive drug responses**

Blood pressure levels are homeostatically maintained through complex interactions of many biochemical, physiological and anatomical traits organized into interrelated systems that exert redundant and counterbalancing pressor and depressor effects [10]. Although single factors may rarely cause blood pressure to deviate into the hypertensive range [11–13], most hypertension has a multifactorial aetiology that includes many genetic and environmental factors acting through the intermediate systems regulating blood pressure level [10].
Antihypertensive drugs lower blood pressure by acting on specific targets within these intermediate systems (Table 1). Since many components of the systems are proteins that may vary in structure, configuration, or quantity because of genetic differences among individuals, it is reasonable to expect that interindividual variation in blood pressure responses to these drugs would in part be genetically determined. Obvious candidate genes to influence blood pressure responses are those that code for components of a system targeted by the drug. Additional candidates are genes that code for components of the counter-regulatory systems opposing an initial drug-induced fall in blood pressure.

Diversity in responses to antihypertensive therapy is well-documented [14–21]. In one study conducted by the Veterans Affairs Cooperative Study Group on Antihypertensive Agents, men with diastolic blood pressures of 95–109 mmHg were randomly assigned to treatment with one of six antihypertensive agents (hydrochlorothiazide, atenolol, captopril, clonidine, dil-tiazem or prazosin), each having a different mechanism of action [14,15]. After dosages were titrated upward to achieve maximal effects, the percentage of patients in whom diastolic blood pressure was lowered to <90 mmHg was similar among drugs and was only slightly greater than 50% for most drugs. As in other studies, the systolic and diastolic blood pressure responses to each drug were continuous and unimodally distributed [16,22]; the standard deviation of responses was similar in magnitude to the average response (approximately 10 mmHg); the range of responses was four-to-eight times greater than the average response [14–16,18]; and, for each drug, a sizable percentage of patients (10–20%) had paradoxical increases in blood pressure [16,20,22]. In most crossover comparisons of individual patients, response to one drug did not reliably predict response to another drug with a different mechanism of action [19–21,23,24].

Progress towards identifying individual patient characteristics that predict blood pressure response prior to drug administration has been limited [25]. Although higher pretreatment blood pressure level is associated with greater antihypertensive drug response, the relationship is not specific to a particular antihypertensive drug or drug class, nor is it correlated with other patient characteristics [26,27]. African Americans are reported to be more responsive to diuretics and calcium channel blockers and less responsive to β-blockers and angiotensin converting enzyme inhibitors than their Cauca-

### Table 1  Antihypertensive drug classes and targets

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Primary Target/Action(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-adrenergic blockers</td>
<td>Block postsynaptic α₁-adrenoceptors</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Inhibit angiotensin converting enzyme</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Block angiotensin II receptors (type 1)</td>
</tr>
<tr>
<td>β-adrenergic blockers</td>
<td>Block postsynaptic β-adrenoceptors</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Block L-type calcium channels</td>
</tr>
<tr>
<td>Central α-agonists</td>
<td>Stimulate α-adrenoceptors in brain stem</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>Increase K⁺ permeability; stimulate cGMP in VSM</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Inhibit renal sodium transporters</td>
</tr>
</tbody>
</table>

cGMP, cyclic guanosine monophosphate; VSM, vascular smooth muscle.
sian counterparts [14,25,28–30]; however, neither gen-
der, nor age, nor measures of body size has been found
to predict response [25,31–34]. While some advocate
measurement of plasma renin activity, indexed to
sodium intake, to aid selection of antihypertensive drug
therapy [35–37], other investigators find this approach
no more predictive than simply determined character-
istics of race and age [38,39]. Consequently, no pro-
fiing method is currently recommended as a basis for selec-
tion of antihypertensive drug therapy in individual
patients [40].

**Classical pharmacogenetics: genes with large
effects on drug metabolism.**

Many classical pharmacogenetic investigations were
initiated by serendipitous observation of an unexpected
drug response, such as an exaggerated response or
complete lack of response [41]. Unrelated individuals
were then studied to verify a bimodal (or multimodal)
distribution of the drug response. Next, families of
individuals from the opposite extremes of the distribu-
tions were evaluated to determine whether the unusual
response phenotype was transmitted from generation to
generation in a pattern consistent with Mendelian
inheritance of a single gene disorder. Finally, modern
techniques of molecular genetics introduced in the late
1980s made it possible to clone genes responsible for
such discretely distributed differences in drug re-
ponses [42]. Three of these single gene polymorph-
isms, summarized in Table 2, are responsible for large
interindividual differences in the metabolism of several
antihypertensive agents. To our knowledge, no single
gene polymorphisms have yet been identified that have
large effects on the absorption, distribution, or elimina-
tion of an antihypertensive drug.

Although single gene polymorphisms with large effects
on drug metabolism have been at the forefront of
pharmacogenetic investigation since its inception [41],
several factors diminish their relevance to contemporary
clinical practice. First, the antihypertensive drugs meta-
bolized by the polymorphic enzymes in Table 2 are no
longer widely used. Second, newer antihypertensive
agents found to be associated with large interpatient
differences in the metabolism of several
antihypertensive agents, and to our knowledge, no single
gene polymorphisms have yet been identified that have
large effects on the absorption, distribution, or elimina-
tion of an antihypertensive drug.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Gene</th>
<th>Antihypertensive drug</th>
<th>Clinical consequence</th>
<th>Other drugs metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debrisoquine hydroxylation</td>
<td>Cytochrome P450 CYP2D6</td>
<td>Alprenolol, Bufuralol</td>
<td>Poor metabolizers: excessive â-blockade</td>
<td>Antiarrhythmics: encainide, flecainide, mexiletine, propafenone</td>
</tr>
<tr>
<td>Chromosome 22</td>
<td>Metoprolol</td>
<td>Propranolol</td>
<td>Extensive metabolizers: loss of blood pressure control</td>
<td>Antidepressants: amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, neuroleptics: perphenazine, risperidone, thioridazine</td>
</tr>
<tr>
<td>N-acetylation</td>
<td>N-acetyltransferase</td>
<td>Hydralazine</td>
<td>Slow acetylators: antinuclear antibodies and systemic lupus erythematosus-like syndrome</td>
<td>Antiarrhythmics: procainamide, antidepressant: phenelzine</td>
</tr>
<tr>
<td>Chromosome 8</td>
<td>Anti-infectives: dapsone, isoniazid</td>
<td>Rapid acetylators: higher dose required for blood pressure control</td>
<td>Anti-inflammatories: P-salicyclic acid, sulfasalazine</td>
<td></td>
</tr>
<tr>
<td>Catechol-O-methylation</td>
<td>Catechol-O-methyltransferase</td>
<td>Methyldopa</td>
<td>Low methylators: lower dose required for blood pressure control</td>
<td>Antiparkinonian: levodopa</td>
</tr>
<tr>
<td>Chromosome 22</td>
<td>Catechol-O-methylation</td>
<td>N-acetyltransferase</td>
<td>N-acetylation</td>
<td>Antihypertensives: RAS inhibitors, ACE inhibitors</td>
</tr>
</tbody>
</table>

Table 2: Single gene polymorphisms with large effects on the metabolism of antihypertensive medications.
[84–86]. Furthermore, at usual therapeutic dosages, the magnitude of blood pressure lowering is similar for drugs within a class [14,18,23], despite considerable differences in their pharmacokinetic properties [87–91]. Finally, when chronic antihypertensive therapy is interrupted, blood pressure-lowering effects often persist long after the drug is eliminated from the body [92,93]. Consequently, there has been major interest in identifying genes that influence the pharmacodynamic determinants of blood pressure response [94,95]. Some progress is being made using candidate gene and genome scanning approaches.

**Candidate gene studies**

*α-Adducin gene*

Adducin is an α/β heterodimeric cytoskeletal protein of the actin–spectrin lattice that is involved in signal transduction. Point mutations in the α-adducin gene explain up to 50% of the difference in blood pressure level between Milan normotensive and Milan hypertensive rats, a genetically hypertensive strain of rats in which increased renal sodium reabsorption plays a major pathophysiological role [96,97].

Cusi and colleagues reported linkage between markers at the human α-adducin locus and a gene contributing to hypertension [6] and found that a variant allele, characterized by a glycine-to-tryptophan change at amino acid 460 of α-adducin (Trp460), was significantly more frequent in 477 hypertensive patients than in 332 normotensive control subjects. Because variants of the α-adducin gene are associated with increased renal tubular reabsorption of sodium and a volume-expanded sodium-sensitive form of hypertension in rats [98], the investigators tested whether the Gly460Trp polymorphism was associated with differences in the antihypertensive response to diuretic treatment with furosemide (40 mg orally every 6 h for three doses) or hydrochlorothiazide (12.5–25 mg orally once daily for 8 weeks). In both protocols, the average blood pressure reduction was more than two times greater in heterozygotes carrying the Trp460 variant than in Gly460 homozygotes [6]. These findings were confirmed in a subsequent trial [99], supporting the contention that the α-adducin polymorphism may be useful in identifying a subset of ‘salt-sensitive’ hypertensive patients more responsive to diuretic therapy [6,99]. The findings also demonstrate how a gene that contributes to hypertension via a particular physiological mechanism (namely, increased renal sodium reabsorption and volume expansion) can serve as a candidate to influence blood pressure response to an antihypertensive agent that targets this mechanism [100].

**Renin–angiotensin system genes**

Hypertensive subjects carrying the Trp460 variant of α-adducin had lower mean plasma renin activity than Gly460 homozygotes [6,98,99], which is consistent with the notion that individuals with ‘low renin’ hypertension are more responsive to diuretic therapy than those with normal or high renin hypertension [35,101,102]. Since the antihypertensive effectiveness of diuretic therapy is inversely related to the degree of counter-regulatory activation of the renin–angiotensin–aldosterone (RAA) system [35,100,103], it is reasonable to hypothesize that variation in genes of the system [5,104–108] may be predictive of variation in blood pressure response. In partial support of this possibility, blood pressure responses to changes in dietary sodium intake were associated with polymorphisms of the genes coding for angiotensinogen and angiotensin converting enzyme (ACE) in some studies [109–113]. Unexpectedly, one of the allelic variants found to be associated with greater blood pressure reduction in response to dietary sodium restriction [109,110] was previously associated with increased, not diminished, activity of the RAA system [5,104,105].

Variation in genes of the RAA system has also been investigated in relation to antihypertensive responses to ACE inhibitors, β-blockers, and calcium channel blockers (Table 3). Among hypertensive patients treated with ACE inhibitors (captopril, enalapril, lisinopril or perindopril), the T235 allele of the angiotensinogen gene was associated with significantly greater systolic and diastolic blood pressure reductions in one study [114,115]. However, the insertion/deletion (I/D) polymorphism of the ACE gene was not associated with differences in blood pressure responses to ACE inhibitors, a β-blocker (atenolol), or a dihydropyridine calcium channel blocker (nifedipine) [114–117]; nor was a polymorphism of the angiotensin II (AT) receptor type 1 gene (A1166 to C) associated with differences in blood pressure response to ACE inhibitors [114]. Recently, a silent polymorphism in exon 5 of the gene coding for the α-subunit of Gα-protein (FokI +/−), which couples β-adrenoreceptors to cAMP production, was reported to be associated with differences in blood pressure response to β-blockers [118].

A variety of other cardiovascular responses to antihypertensive drug therapy have been investigated in relation to polymorphisms in the genes coding for ACE and the AT1 receptor (Table 4). Overall, early results support the notion that genetic variation may have pleiotropic effects on numerous biochemical, physiologic, and anatomic measures of response to antihypertensive drug therapy [116,117,119–132].

**Genome scanning studies**

For many traits, there may be no known polymorphic candidate gene or the list of plausible candidates may be so extensive as to render investigation of each one impractical. In these circumstances, a genome scanning
approach can be used to first identify chromosomal regions containing genes influencing the trait, followed by positional cloning of candidate gene(s) within linked regions [133, 134]. Generally, such an approach employs highly polymorphic markers of DNA sequence variation throughout the genome measured in biologically related family members. Linkage analyses then assess coinheritance of the markers with chromosomal regions containing genes influencing the trait [135]. Because no prior knowledge or assumptions are required about gene function, one attractive feature of this approach is the possibility of identifying new genes previously unsuspected to influence the trait. Moreover, the relative strength of linkage evidence accompanied by already-available knowledge about functions of genes within the linked regions, can serve to prioritize the subsequent search for functional mutations in the positionally implicated genes. However, because this method requires that the trait of interest be measured in a large number of related individuals (for example, sibling pairs), it poses significant logistical challenges for antihypertensive drug response traits in humans.

To our knowledge, the only published genome-wide scan for a pharmacogenetic trait locus employed a rodent model of genetic hypertension to identify a region of rat chromosome 2 containing a gene influencing blood pressure response to blockade of voltage-dependent L-type calcium channels [136]. In this study, Vincent and colleagues performed linkage analyses using 40 different microsatellite markers measured over 15 chromosomes. For eight of 11 markers on chromosome 2, the reduction in blood pressure in response to the calcium channel blocker was significantly greater in animals homozygous for the allele from hypertensive rats than in heterozygous rats. Maximum LOD scores of 4.4 and 4.1 for the systolic and diastolic blood pressure responses, respectively, were observed between two markers, D2Wox8 and D2Mit15, with variation at this locus accounting for 10.3 and 10.4% of variation in systolic and diastolic blood pressure responses, respectively [136]. In contrast, no effects of variation at this or other measured loci were seen on baseline blood pressure level or the blood pressure responses to a short-acting ganglionic blocking agent (trimethaphan camsylate) or an angiotensin II receptor antagonist (losartan) [118].

A gene coding for a protein involved in intracellular calcium channels plays a role in determining differences in blood pressure responses to blockade of voltage-dependent L-type calcium channels is consistent with human and animal studies indicating that variation in calcium metabolism plays a role in determining differences in blood pressure responsiveness to blockade of voltage-dependent L-type calcium channels [137].
calcium homeostasis [calmodulin-dependent protein kinase II-delta (Camk)] resides within the linked region and is therefore a candidate to influence blood pressure response to the calcium channel antagonist. Although inferences to human hypertension are speculative, this study demonstrates the potential for genetic variation to contribute to differences in blood pressure response to specific antihypertensive agents and illustrates how a gene that influences response to a drug with a known mechanism of action can implicate the blood pressure-regulating system targeted by the drug as a contributor to the hypertensive state.

**Future developments**

Mapping and sequencing of all 50,000–100,000 genes in the human genome [138] are expected to be fully completed by the year 2003 [4]. Among the many methodological and technological advancements spawned by these accomplishments, several are likely to expand the role of pharmacogenetics in interventions against hypertension.

**Genome-wide association studies using single nucleotide polymorphisms**

One capability that will facilitate the discovery of genes influencing drug responses in humans is the ability to perform genome-wide association studies using single nucleotide polymorphisms (SNPs). SNPs are positions in the genome at which two alternative nucleotides occur at an appreciable frequency (>1%). As the most abundant form of polymorphism in the human genome, SNPs are estimated to occur every 500–1000 bp [139]; thus, there are more than three million SNPs per human genome (which consists of approximately $3 \times 10^9$ bp). Genetic maps are now being constructed with >2000 SNPs at an average spacing of <2 cM between variable sites [140] (1 cM $\approx 100,000$ bp). In contrast, the ‘variable number of tandem repeat’ (VNTR) marker sets now used for genome-wide searches generally include 300–400 markers spaced every 10 cM. It has been calculated that a collection of 1000 biallelic SNPs provides the same power to detect a QTL as conventional sets of 300–400 multi-allelic VNTR markers [141]. Moreover, for linkage studies to achieve adequate power to detect QTLs with small or moderately sized effects, very large samples of related family members must be studied [142], clearly, a sample design that is unfeasible for most drug response traits. Association studies that utilize biallelic SNPs measured in biologically unrelated individuals not only are inherently more powerful, but also require fewer study subjects, and thus are the only practical study design for genetic analyses of antihypertensive drug responses in humans. Dense SNP maps have the potential to reduce a genome-wide search for a QTL influencing antihypertensive drug responses to a relatively straightforward series of comparisons of allele frequencies between groups of unrelated individuals selected from opposite extremes of the drug response distribution [139].

An additional development necessary to make this approach widely applicable is the ability to rapidly genotype large numbers of SNPs at a reasonable cost. Two-dimensional arrays of chemically synthesized oligonucleotides attached to a glass surface (so-called DNA chips) appear to offer one possible approach [140,143]. Such chips are already commercially available to assess known mutations in the human cytochrome P450 genes encoding the CYP2D6 and CYP2C19 enzymes responsible for metabolizing many commonly prescribed drugs. Standardization and commercialization of this technology should reduce costs and extend its applicability [144,145]. A further challenge is the development and implementation of efficient methods of cataloging and analysing the massive amounts of genotypic data that can be generated [146].

**Genotyping in large-scale clinical trials**

Collection and analysis of genotype information is likely to become a routine part of large antihypertensive drug trials designed to assess blood pressure lower-

**Table 4 Candidate gene studies of other cardiovascular responses**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Drug</th>
<th>Response phenotype</th>
<th>Sample description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme</td>
<td>Insertion/deletion</td>
<td>ACE-I</td>
<td>Cough</td>
<td>EHT, CHF</td>
<td>[119, 120]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma ACE</td>
<td>NT</td>
<td></td>
<td>[121]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma ACE</td>
<td>EHT</td>
<td></td>
<td>[122]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT, R mRNA</td>
<td>EHT</td>
<td></td>
<td>[123]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal plasma flow</td>
<td>NT</td>
<td></td>
<td>[124]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteinuria</td>
<td>PRN</td>
<td></td>
<td>[117, 125–128]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LV mass</td>
<td>EHT</td>
<td></td>
<td>[116]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic filling</td>
<td>EHT, CRF</td>
<td></td>
<td>[116, 117, 129]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerular filtration</td>
<td>nDRD</td>
<td></td>
<td>[126, 127, 130]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerular filtration</td>
<td>nDRD</td>
<td></td>
<td>[130]</td>
</tr>
<tr>
<td>Angiotensin II receptor, type 1</td>
<td>A1166C</td>
<td>Phenylephrine, All</td>
<td>Coronary vasoconstriction</td>
<td>CAD</td>
<td>[131]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACE-I, CCB-D</td>
<td>Pulse wave velocity</td>
<td>EHT</td>
<td>[132]</td>
</tr>
</tbody>
</table>

Drug abbreviations are as given in Table 3: All, angiotensin II; AT, R, angiotensin II receptor, type 1; LV, left ventricular; EHT, essential hypertension; CHF, congestive heart failure; NT, normotension; PRD, proteinuric renal disease; CRF, chronic renal failure; nDRD, non-diabetic renal disease; CAD, coronary artery disease.
ing and reduction in clinical cardiovascular disease events, including stroke, myocardial infarction and progression of renal disease. Genotyping study participants can be viewed as a logical extension of the usual covariate information (such as race, gender, age and body size) collected to assess potential ‘modifiers’ of drug response [147]. One can envision testing the effects of variation in known candidate genes as well as scanning the entire genome to identify loci harboring new genetic variants influencing blood pressure response and the subsequent development of target organ complications. Such studies are already reported to be underway [148–153].

Not all of the variation in target organ complications among hypertensive individuals can be predicted by measurements of blood pressure [154–156]. Even if equally hypertensive individuals have their blood pressures lowered to the same level, there may still be residual genotype-dependent variation in measures of target organ disease. Although our current trial and error approach to antihypertensive drug therapy can be effective in controlling blood pressure [23,24], a ‘wait-and-see’ approach to the prevention of target organ complications is difficult to defend. Genetic measurements, which need only be made once in a person’s lifetime, appear to be well-suited for evaluation and potential use as predictors of clinical events that may take decades to develop but have their origins early in life.

Individualized drug therapy
An ultimate goal of pharmacogenetic knowledge is to advance beyond the current ‘one size fits all’ approach to antihypertensive drug therapy to more individualized approaches. Since proteins are the targets of antihypertensive drugs, the complete mapping and sequencing of all genes in the human genome [4] implies that potential targets of virtually every antihypertensive drug will be discovered. The challenge will be to ascertain the functions of many newly discovered genes, assess the extent and impact of their polymorphisms, and identify those whose gene products are valid drug targets [149,157,158]. The latter task will be aided by identification of genes that influence disease activity, inasmuch as disease genes may be candidates to influence drug response. Conversely, drug response genes may become candidates to influence disease process. The ability to obtain complete ‘molecular profiles’ of disease and drug response genes in individual patients [159] should provide efficient and highly accurate methods to identify individuals prior to drug administration who are likely to have favourable or unfavourable responses to treatment with a particular drug or class of drugs [160]. Reliable methods to ensure that a drug is only administered to those in whom it will be effective and non-toxic may also serve to maintain the usefulness of drugs that are found to be toxic in a few but are efficacious in many others [161].

Knowledge of genes that contribute to the disease process and genes that influence drug responses will facilitate the development of new drugs and therapeutic approaches that are based on a deeper understanding of the molecular determinants of the disease and the response to therapy. Drugs that are more specific for the molecular characteristics of individual patients should contribute to greater efficacy and reduced toxicity. Certainly, the collection and analyses of unprecedented amounts of genetic information in the coming years has the potential to revolutionize the way drugs are developed and the approaches taken to diagnose, treat and prevent hypertension and its associated target organ diseases.

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