Genetics of Hypertension, Target-Organ Complications, and Response to Therapy

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This issue of Circulation honors extraordinary achievements in cardiovascular disease research during the past half century and their impact on the prevention, evaluation, and treatment of cardiovascular disorders. One area of particularly noteworthy advancement has been that of hypertension, the most prevalent risk factor for diseases of the heart, brain, and kidneys and one of the most common indications for prescription medications. Because essential hypertension, defined by systolic blood pressure levels $\geq 140$ mm Hg or diastolic blood pressure levels $\geq 90$ mm Hg, was the subject of a comprehensive 2-part review recently published in Circulation, this article will focus on 3 frontiers of hypertension research that are undergoing particularly rapid advancement and are poised to experience further profound developments with completion of the Human Genome Project. These areas include new understanding of the genetic causes of hypertension, the genetic susceptibility to target-organ complications, and the pharmacogenetics of antihypertensive therapy. In each of these areas, our objectives are to review present knowledge by highlighting salient findings and to suggest where future advancements are likely to improve the prevention, evaluation, and treatment of hypertension.

Genetic Causes of Hypertension

Previous studies have yielded consistent and significant estimates of the genetic contribution to interindividual differences in both systolic and diastolic blood pressure levels. For example, in a sample of 1266 individuals in 278 non-Hispanic white pedigrees, the heritability of systolic blood pressure level (that is, the proportion of interindividual variation attributable to genetic differences among individuals) was estimated to be 0.37. Similar values have been reported for diastolic blood pressure level. Contemporary genetics research has advanced from the general recognition that "genes necessarily have the same blood pressure level; therefore, multiple genes potentially influence interindividual differences in blood pressure level. Because blood pressure control involves a redundancy of traits with balancing pressor and depressor roles, the impact of any one gene may be reduced as its effect is transmitted across intervening levels of biological organization. In addition, the complexity of blood pressure regulation suggests that there is substantial genetic heterogeneity. Hence, individuals with the same blood pressure level do not necessarily have the same genotype at relevant loci, nor do individuals with the same genotype at particular loci necessarily have the same blood pressure level.

Recent studies have demonstrated genetic linkage and association between marker loci and candidate genes that potentially influence blood pressure level. For example, both Jeunemaitre and colleagues and Caulfield and colleagues reported positive linkage between variants at the angiotensinogen gene locus and a gene contributing to essential hypertension. Jeunemaitre followed up this linkage result with an association study between several variant loci in the angiotensinogen gene and essential hypertension. In particular, the frequency of an M$\rightarrow$T substitution at codon 235 of angiotensinogen was associated with essential hypertension in 2 separate samples. Associations between the angiotensinogen gene polymorphism and essential hypertension have been verified by some, but not by others. It is generally believed that the original association attributed to the M235T polymorphism was due to its linkage disequilibrium with a polymorphism at position $-6$, which is now known to influence transcription levels of the AGT gene.

Even though a role for genetic variation in determining interindividual differences in blood pressure level and diagnostic category is no longer questioned, the identity of the contributing genes and their mechanism of action remain elusive. As already reviewed, Lifton and colleagues have made spectacular advances in identifying single genes underlying several rare mendelian forms of hypertension. Although the low frequency in the general population diminishes their public health impact, the contribution of these variants to understanding genetic pathways of blood pressure regulation is considerable. In particular, identification of genetic variants with large effects on pathways of blood pressure control provides direction to novel points for inter-

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vention, as exemplified by discovery of LDL-receptor mutations underlying familial hypercholesterolemia and the ultimate development of effective statin drugs. Despite successes in identifying genes for rare mendelian forms of hypertension, progress toward identifying and characterizing genes contributing to hypertension in the general population has been much more modest.

As a complement to biological candidate gene studies, genome-wide linkage analyses are now considered the method of choice for identifying hypertension susceptibility loci. We have completed the first genome-wide linkage analyses to identify loci linked to genes influencing blood pressure levels in the population at large. Multipoint linkage analyses of the 22 autosomes identified 4 regions showing significant linkage to genes that influence systolic blood pressure level. The 4 regions are located on chromosomes 2, 5, 6, and 15. One region identified by this genome-wide linkage analysis, 5q33 to 5q35, contains multiple candidate genes, including genes that encode the β2-adrenergic receptor, the α2-adrenergic receptor, and the dopamine receptor. We have resequenced each of these genes to identify the spectrum of DNA variation in the population sampled and carried out a series of association studies to identify which of these positional candidate genes is influencing interindividual variation in blood pressure level and diagnostic category (ie, hypertension versus normotension). The results of these positional candidate gene studies indicate that the Arg16Gly and Gln27Glu polymorphisms in the β2-adrenergic receptor gene (ADRB2) are influencing blood pressure levels and diagnostic category in Rochester, Minn. For example, the frequencies of both the Gly16 and Glu27 alleles were higher in hypertensives than in normotensives (0.649 versus 0.604 and 0.490 versus 0.429, respectively), and the odds ratio for the occurrence of hypertension was 1.80 for the Glu27 allele. Moreover, an ADRB2 knockout mouse has been reported to have elevated blood pressure level, and the Arg16Gly and Gln27Glu substitutions have been shown to alter β2-adrenergic receptor function in vitro.

The genome-wide linkage scan discussed above is but an early ripple before a coming tidal wave of studies designed to localize genes for cardiovascular disease and its risk factors, including blood pressure. Sequencing of the human genome by both public and private efforts is rapidly progressing, as is the identification of sequence variation. It is therefore imperative that progress be made in placing this flood of genetic information in the context of contemporary medical practice by studying genotype-phenotype relationships.

Genetic Susceptibility to Target-Organ Damage

A working hypothesis regarding genes that contribute to development of hypertension-related target-organ diseases is illustrated in Figure 1. First, there may be genes that do not directly influence blood pressure but that cause primary disease of a target organ (eg, 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 (dashed arrow in Figure 1). 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 (eg, 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 (eg, gene 3). The potential for pathogenetic factors and pathological mechanisms that cause hypertension to also lead to target-organ complications is emphasized by the observation that many vasoconstrictor, antinatriuretic, and neuroexcitatory substances—notably angiotensin II, norepinephrine, and endothelin—not only raise blood pressure but also stimulate remodeling and growth. With the exception of cardiac hypertrophy, most of the other target-organ complications of hypertension are the consequences of chronic ischemia resulting from atherosclerosis of the conduit arteries delivering blood to the organ and arteriolosclerosis of the small muscular resistance arteries within the target organ (Table).

Arteriolosclerosis involves small muscular resistance arteries within a target organ, whereas atherosclerosis involves larger elastic conduit arteries that supply blood to the organ. Arteriolosclerosis is characterized by thickening of the media of the vessel due to remodeling, hypertrophy, and/or hyperplasia of smooth muscle, whereas atherosclerosis is characterized by hyperplasia and remodeling primarily involving intimal cells. Research studies are beginning to identify genes that contribute to the cardiac and macrovascular and 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.

Among patients with hypertension, echocardiographic measures of left ventricular mass and geometry are powerful, independent predictors of clinical cardiovascular disease end-point events. The direct, continuously graded relationship between blood pressure levels and left ventricular mass and the consistent association of hypertension with left ventricular hypertrophy imply that pressure levels are a major determinant of left ventricular mass. Presumably, left ven-

Manifestations of Ischemic Target-Organ Damage in Hypertension

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<th>Target Organ</th>
<th>Arteriolosclerosis</th>
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<td>Heart</td>
<td>Microvascular disease</td>
<td>Myocardial infarction</td>
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<td>Brain</td>
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tricular hypertrophy is a structural compensatory response to increased mechanical load and wall stress. Other implicated determinants of left ventricular mass have included race, sex, age, body size, dietary sodium intake, blood viscosity, and measures of sympathetic neuron system and renin-angiotensin-aldosterone system activity.

Left ventricular mass is a complex phenotype influenced by the interacting effects of multiple genetic and environmental factors. Twin and family studies have estimated the heritability of the left ventricular mass as between 22% and 59%. In genetically hypertensive rats, the heritability of left ventricular mass was estimated to be 76%, and 2 quantitative trait loci influencing heart weight were mapped to rat chromosome 1. Interestingly, one of these influences only heart weight, and the other influenced both heart weight and blood pressure level. Thus, genetic variation probably contributes to interindividual differences in the left ventricular mass by virtue of effects on blood pressure level as well as via pathways that are not captured by measurements of blood pressure. It is possible that identification of genes that influence left ventricular mass may enhance the ability to identify genes that influence blood pressure, because left ventricular mass provides a more stable, anatomic measure of the average, integrated effects of blood pressure over a prolonged period of time.

Consistent with the distinctions between atherosclerosis and arteriolar sclerosis mentioned above, 2 forms of ischemic cerebrovascular disease are recognized: cortical infarction and subcortical ischemia. Subcortical ischemia is far more common than cortical infarction and is readily distinguishable on magnetic resonance imaging (MRI). Ischemic change in the subcortical white matter, referred to as leukoaraiosis, results from impaired blood flow in the long penetrating arterioles, whereas an occlusion in the distribution of the short penetrating arterioles produces lacunar infarction in the deep gray nuclei. Subcortical white matter ischemic change and lacunar infarctions tend to occur in the same persons and are ascribed to similar pathogenetic mechanisms.

Strong evidence for genetic variance in MRI measures of leukoaraiosis was recently provided by a study of normal elderly male twins. Brain MRI scans (1.5 T) were obtained from 74 monozygotic (MZ) and 71 dizygotic (DZ) white male twins who were 68 to 79 years old 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% CI, 66% to 76%). Proband concordance rates for large volumes of leukoaraiosis (ie, >10 cm³) were 61% in MZ twins and 38% in DZ twins, compared with a prevalence of 15% in the entire sample.

Despite considerable literature supporting a genetic contribution to manifestations of atherosclerotic cerebrovascular disease, few studies have attempted to identify genes that contribute to manifestations of arteriolar sclerosis cerebrovascular disease. One case-control study from Japan suggested an association of lacunar infarction with the deletion (D) allele of the insertion/deletion polymorphism of the gene coding for ACE in a small sample. Another reported an association with the T677C polymorphism of the methylenethylenediamine-2-carboxylate reductase gene. Intriguingly, mutations in the human Notch3 gene on chromosome 19p13 have been identified to account for the rare mendelian disorder of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Although hypertension is not a feature of the disorder, it is characterized by small-vessel and neuropathic changes reminiscent of those that underlie leukoaraiosis.

Hypertension may be a consequence as well as a frequent cause of renal dysfunction. Among 332,544 men screened for the Multiple Risk Factor Intervention Trial (MRFIT), there was a graded relationship between levels of both systolic and diastolic blood pressure at baseline and risk of subsequent end-stage renal disease (ESRD), even after other predictors of ESRD risk (age, race, smoking, cholesterol, diabetes, myocardial infarction, and income) had been considered. The risk of ESRD is greater among minority populations, particularly among Mexican Americans and blacks. The most common renal pathological change associated with nonmalignant hypertension is hyalinization and sclerosis of the walls of preglomerular (afferent) arterioles, referred to as hypertensive nephrosclerosis.

Familial aggregation of ESRD, including hypertensive ESRD, has been documented both in blacks and whites. In pursuit of human renal failure susceptibility genes, Freedman and colleagues conducted linkage studies in black families affected by ESRD. Markers on chromosome 10q spanning the homologous region of the rodent Rf-1 gene did not show evidence for linkage to ESRD; however, 2 adjacent markers on chromosome 10p approached significance in sib pairs with nonidiabetic ESRD. In other samples, evidence of linkage approached significance for the gene coding for transforming growth factor-β, and evidence of statistically significant association was found for alleles at the plasma kallikrein gene. However, the most direct evidence of renal failure susceptibility genes comes from studies of the fawn-hooded rat. Two genes, designated Rf-1 and Rf-2, were determined to contribute substantially to the development of renal impairment. Rf-1 explained 40% of the genetic component of renal impairment but showed no significant linkage or association with blood pressure levels, suggesting that the Rf-1 locus acts through a mechanism other than by increasing blood pressure. The second gene, Rf-2, mapped to a locus that influences blood pressure but also appeared to influence renal damage through a mechanism different from blood pressure.

**Antihypertensive Pharmacogenetics**

A variety of mechanisms determine drug response. Pharmacokinetic mechanisms that determine the level of the drug in the blood, and ultimately at its target, include drug absorption, distribution, excretion, and metabolism. 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 events that occur. 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. Knowledge of genes that influence the pharmacodynamic determinants of blood pressure response to...
anthypertensive medications has the potential to provide new insights not only into molecular mechanisms that influence drug response but also into the role that these genes may play in determining interindividual differences in blood pressure and the occurrence of hypertension.

Although single-gene polymorphisms with large effects on drug metabolism have been at the forefront of pharmacogenetic investigation since its inception, several factors diminish their relevance to contemporary antihypertensive drug therapy. First, agents that are metabolized predominantly by known polymorphic enzymes with large interindividual differences in activity are no longer widely used (for example, hydralazine and α-methyldopa). Second, for most antihypertensive drugs now in common use, pharmacodynamic mechanisms play the predominant role in determining interindividual variation in blood pressure responses. For example, the dose-response relationships for most modern antihypertensive drugs are flat, and the magnitude of blood pressure lowering is similar for drugs within a class. Despite considerable differences in their pharmacokinetic properties, Consequently, there has been major interest in identifying genes that influence the pharmacodynamic determinants of blood pressure response.

Cusi and colleagues reported linkage between markers at the human α-adducin locus and a gene contributing to hypertension 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, the investigators tested whether the Gly460Trp polymorphism in humans with essential hypertension was associated with differences in the blood pressure response to diuretic treatment with furosemide or hydrochlorothiazide. In both protocols, the average blood pressure reduction was greater in heterozygotes carrying the Trp460 variant than in Gly460 homozygotes. These findings were confirmed in a subsequent study, 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. These investigations 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 gene to influence blood pressure response to an antihypertensive agent that targets this mechanism.

For many traits, there may be no known polymorphic candidate gene, or the list of possible candidates may be so extensive as to make investigation of all of them impractical. In this circumstance, a genome scanning approach can be used to first identify the chromosomal regions of genes that influence the trait, followed by positional cloning of candidate gene(s) within the linked regions. Because prior knowledge or assumptions are required about gene function, the attractive feature of this method is the possibility of identifying new genes previously unsuspected to influence the trait. To the best of our knowledge, the only published genome-wide search for a pharmacogenetic trait locus used a rodent model of genetic hypertension to identify a region on rat chromosome 2 containing a gene that influences blood pressure response to a dihydropyridine calcium channel blocker (PY108-068).

Future Developments

As a consequence of the Human Genome Project, complete mapping and sequencing of all 50 000 to 100 000 genes in the human genome are expected to be completed before the year 2003. Among the many methodological and technological advancements spawned by these accomplishments, several are likely to expand the role of genetics in hypertension-related research.

One capability that will facilitate the discovery of genes that influence the human hypertension-related phenotypes described above is the ability to perform genome-wide association studies using single-nucleotide polymorphisms (SNPs). Association studies that use 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 many hypertension-related phenotypes—in particular, antihypertensive drug responses. Dense SNP maps have the potential to reduce a genome-wide search for a gene that influences a hypertension-related phenotype to a relatively straightforward series of comparisons of allele frequencies between groups of unrelated individuals selected from opposite extremes of the phenotypic distribution.

Collection and analysis of genotype information is likely to become a routine part of large clinical trials, especially those designed to assess blood pressure lowering and reduction in clinical cardiovascular disease events, such as myocardial infarction, stroke, and progression of renal disease. Genotyping of study participants can be viewed as a logical extension of the usual covariate information (such as race, sex, age, and body size). 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 that influence blood pressure, development of target-organ complications, and responses to antihypertensive drug therapy.

The ultimate goal of genetic knowledge is to advance beyond our current “one-size-fits-all” approaches to more individualized prevention, evaluation, and treatment of hypertension and its target-organ complications. The anticipated mapping and sequencing of all genes in the human genome implies that all of the genetic factors that contribute to interindividual variation in these phenomena will be discovered. The challenge will be to ascertain the functions of newly discovered genes, to assess the extent and impact of their polymorphisms, including gene-gene and gene-environment interactions, and to identify those pathways of effect that are valid targets for intervention. Discovery of genes that influence the development and progression of disease and discovery of genes that influence responses to antihypertensive therapy are reciprocal processes, inasmuch as disease genes become candidates to influence response to therapeutic interventions and response genes become candidates to influ-
ence disease activity. Knowledge of genes that contribute to the disease process and genes that influence therapeutic responses should also 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. Certainly, the collection and analyses of unprecedented amounts of genetic information in the coming years have the potential to revolutionize the approaches to the prevention, evaluation, and treatment of hypertension and its associated target-organ diseases.

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