Genetic Determinants of Hypertension: An Update

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Hypertension represents a global public health burden. In addition to the rarer Mendelian forms of hypertension, classic genetic studies have documented a significant heritable component to the most common form, essential hypertension (EH). Extensive efforts are under way to elucidate the genetic basis of this disease. Recently, a new form of Mendelian hypertension has been identified, pharmacogenetic association studies in hypertensive patients have identified novel gene-by-drug interactions, and the first genome-wide association studies of EH have been published. New findings in consomic and congenic rat models also offer new clues to the genetic architecture of this complex phenotype. In this review, the authors summarize and evaluate the most recent findings related to hypertension gene identification.

Introduction

Hypertension and its related complications represent and contribute to the leading cause of morbidity and mortality in the Western world. Hypertension affects 25% to 30% of people in the United States and similar numbers exist for populations around the world [1,2]. Clinically significant implications arise, as the presence of hypertension is a strong predictor and risk factor for stroke, congestive heart failure, coronary heart disease, peripheral vascular disease, and end-stage renal disease and death in the elderly [3,4].

Despite being the focus of intense research efforts, our understanding of the disease mechanisms, particularly those related to the most common form of hypertension, known as essential hypertension (EH), are still limited. Classic genetic studies have documented a significant heritable component to EH [5–8]. Consequently, extensive efforts are under way to elucidate the genetic basis of this disease. The first breakthroughs in the genetics of EH came through the study of rare, familial monogenic forms. However, as these forms offered limited insights into EH, linkage analysis became the primary method of candidate gene identification. With the availability of single nucleotide polymorphisms (SNPs) in the late 1990s, candidate gene association studies became a commonly used method in the hunt for EH genes. In the past few years, further advances in microarray technology and statistical genetics have allowed the association approach to be extended to the full genome. Genome-wide association (GWA) studies are now technically and economically feasible, and several groups are applying this approach to the search for EH genes. In this review, we summarize and evaluate the most recent findings (published within the past 3 years) related to hypertension gene identification.

New Findings in Monogenic Hypertension

Rare monogenic disorders that follow a Mendelian mode of inheritance represent distinct forms of hypertension particularly amenable to gene identification given current technologies. Several monogenic forms of familial hypertension have been linked to the genome and their causal mutations subsequently discovered [9–15].

Most recently, a novel form of Mendelian hypertension secondary to aldosteronism was found by Geller et al. [16]. The authors reported a father and two daughters with severe, early-onset hypertension similar to patients with glucocorticoid-responsive aldosteronism (GRA); however, unlike GRA patients, treatment with dexamethasone failed to normalize blood pressure levels. Despite clinical features resembling GRA, subsequent genetic testing of the three family members excluded a mutation at the aldosterone synthase locus, the genetic defect behind GRA, and the genetic cause remains unknown. An analysis of the extended pedigree of this family supports autosomal dominant transmission. The authors suggested that identification of the causative genetic defect in this family will enable new insights into the regulation of adrenal steroid biosynthesis.

Although it is important to note that Mendelian disease alleles are extremely rare and only account for

less than 1% of the cases of hypertension in the general population [17], increasing evidence shows that the genes and variants found through the study of these monogenic forms may have an effect on common blood pressure regulation [18]. Using more than 2000 adults from 520 families characterized for 24-hour ambulatory blood pressure and various cardiovascular traits, Tobin et al. [18] genotyped 298 tagging and potentially functional SNPs from 11 genes underlying monogenic forms of hypertension and hypotension. The authors identified associations for several blood pressure phenotypes with a number of SNPs in the *KCNJ1* gene, an inwardly-rectifying potassium channel gene mutated in Bartter syndrome, type 2. In addition, they observed significant associations between blood pressure and variants in several of the other Mendelian hypertension and hypotension disease genes. Although these results await replication in an independent population, the authors concluded that common variants in genes responsible for monogenic forms of both hypertension and hypotension may affect blood pressure levels in the general population.

New Findings in Essential Hypertension

EH is the most common form of hypertension, occurring in 95% of patients diagnosed with hypertension. Although the study of monogenic forms has yielded some insights into EH, there are likely to be many more novel genes and pathways for it yet to be discovered. In contrast to Mendelian forms, essential hypertension is polygenic in nature with many genes contributing a small effect to the phenotype, which makes it more challenging to identify causal mutations. In addition to multiple genetic causes, EH is also known to be an extremely complex phenotype strongly affected by environmental factors such as age, gender, smoking status, diet, exercise, body mass index, and stress. Over the years, a variety of methods have been used in an attempt to uncover genetic loci influencing this phenotype, including linkage, candidate gene association, rodent models, and most recently, genome-wide association (Table 1). We briefly review the latest findings in these areas.

Linkage

Linkage analysis tests for the joint segregation of genomic markers and a particular trait of interest within families. Although it has long-range mapping capability, its statistical power is limited to detecting genes with larger effect sizes. Consequently, as the genetic architecture of EH likely consists of many genes with small-to-moderate effect, this approach has not led to a convincing identification of a novel candidate gene for hypertension. Complementary to linkage analysis, association has shorter range mapping abilities, but is more powerful for the identification of alleles with smaller effect sizes. This approach tests for differences in allele frequencies between unrelated individuals with and without a particular trait. With its greater statistical power for smaller effect sizes, and with recent advances in high-throughput genotyping and statistical analysis, the association approach has increased substantially in popularity over the past 5 years. Nevertheless, numerous populations exist with genome-wide linkage data, and methods for combining this data with that from association analysis are being actively pursued. An elegant example of such an approach is provided by Cheung et al. [19•], where both linkage and association analysis were used to map variants impacting human gene expression phenotypes. The findings from this report, which allow for a comparison between these two methods of gene identification in the same dataset, indicate that using the two approaches together may offer additional information than using either one alone. By performing both linkage and association analysis in the same population, and comparing the results, a better idea about the genetic architecture of a particular phenotype can be obtained. For example, in genomic regions where a quantitative trait locus (QTL) has been mapped by linkage analysis but association analysis fails to find a significant signal, sequencing may be required to identify the causative variant, as it may be rare. It is well established that association analysis has little power to detect rare variants. In a population where only association is performed, regions of the genome with rare variants contributing to the phenotype would likely be missed. Contrary to this, performing only linkage analysis may miss those variants with smaller effect sizes. Currently, genome-wide association is being planned or is under way in numerous hypertensive populations with linkage data. The combination of both genome-wide linkage and association data may offer novel insights into the genetic architecture of EH.

Candidate Gene Association

Over the past several years, the candidate gene association approach has been an immensely popular method for identifying genes involved in hypertension, although replicable results have been difficult to achieve. These studies often suffer from limited sample sizes and a low prior probability of the selected candidate gene(s) being associated with hypertension. Within the past year, numerous candidate gene studies have been published for EH, many examining one or a few genes selected based on their known function, previous association with hypertension, or previous association with related phenotypes. One of the most recent, larger, and more systematic studies was published by Kohara et al. [20]. Using the Millennium Genome Project from Japan and combining a two-stage association design with a novel pathway-oriented selection of candidate genes, the authors identified significant signals in five G-protein–related genes, and they demonstrated interaction between two of them. This approach is unique in that it took a pathway-oriented selection of candidate genes and tested for interaction within these

Table 1. Summary of gene and loci identified for hypertension in humans

Form of hypertension						
Monogenic	**Method of identification**	**Gene [Reference]**	**Chromosome**	**Mode of inheritance**	**Variant and function**	**Comments**
Nonglucocorticoid-remediable aldosteronism		Unknown	Unknown	Autosomal dominant	Unknown	Clinical, biochemical, and pedigree analysis identifies new form of Mendelian hypertension
Essential	Linkage	[19•]				Combining linkage and association data may prove useful in gene identification
	Candidate-gene association / pharmacogenetic association	*RGS20, GNA14* [20]	8, 9	N/A	rs3816772, rs1801258	Potential hypertension candidate pathway identified exhibiting gene-gene interaction
		NPPA [21•]	1	N/A	rs5065	Associated with modification of antihypertensive treatment effects on CVD and BP
		ACE [22]	17	N/A	rs4344	African American homozygote carriers responded significantly faster to ACE inhibition than heterozygotes
		ACE2 [23]	X	N/A	rs2106809	Adjusted DBP response to ACE inhibitors was lower in T allele carriers than in CC genotype carriers
		ADD2 [24]	2	N/A	rs2024458; rs3755375; rs1541582	Three most significant SNPs demonstrating gene-by-drug interactions
	GWA	No genome-wide significant signals were identified [26••]	Strongest signals identified on chr 1 and X chr	N/A	rs2820037 (chr 1); rs5938070 (X chr with expanded set of controls)	Only 1 of 6 signals replicated in FBPP individuals.
		No genome-wide significant signals were identified [28]	Strongest signals identified on chr 1 and chr 8 for SBP and DBP, respectively	N/A	rs10493340 (chr 1); rs1963982 (chr 8)	Replication planned

ACE—angiotensin-converting enzyme; BP—blood pressure; chr—chromosome; CVD—cardiovascular disease; DBP—diastolic blood pressure; FBPP—Family Blood Pressure Program; GWA—genome-wide association; N/A—not available; SBP—systolic blood pressure; SNP—single nucleotide polymorphism.

pathways. It is unlikely that these genes would have been identified through a traditional candidate gene approach. Although the *P* values in this report were not particularly low, and although the results need further verification, the authors concluded that they have identified a candidate-pathway where multiple genes may be interacting to predispose to hypertension.

Other recent notable candidate gene studies include those that assessed response to antihypertensive treatment in relation to particular SNPs. These pharmacogenetic studies were aimed at identifying genetic variation that can ultimately be used to predict drug response and guide therapeutic management of hypertensive patients. In perhaps one of the largest studies examining gene variants and antihypertensive treatment outcomes, Lynch et al. [21•] used data from more than 38,000 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized multicenter clinical trial, to determine if two variants of the atrial natriuretic precursor A (*NPPA*) gene were associated with cardiovascular disease (CVD) and blood pressure lowering among patients randomized to one of four antihypertensive medications. The authors found that the T2238C variant of *NPPA* significantly modified the effects of antihypertensive medication on CVD and blood pressure, in that the genotype at this locus affected the outcome based on class of antihypertensive medication. Specifically, those carrying the minor C allele of this variant had more favorable CVD outcomes when randomized to a diuretic, and those who were TT homozygotes experienced more favorable outcomes when receiving a calcium channel blocker. Consistent with these findings, the study also demonstrated that 6-month changes in systolic and diastolic blood pressure were greater in CC homozygotes when taking a diuretic than when taking a calcium channel blocker, angiotensin-converting enzyme (ACE) inhibitor, or α-adrenergic blocker. Some limitations to this study include the facts that the *NPPA* gene was not comprehensively surveyed and that replication is still needed; however, this report provides an excellent example of the logistical demands of such a study and the value of such research.

Additional pharmacogenetic association studies have also been published recently. Two such studies examined variation in genes within the renin-angiotensin system, angiotensin I–converting enzyme (ACE) 1 and ACE2 [22,23]. Bhatnagar et al. [22] typed three polymorphisms in the ACE gene and examined time to response to ACE inhibitors in 347 African Americans from the African American Study of Kidney Disease and Hypertension (AASK) trial. They found those homozygous for the G12269A SNP or those homozygous for ACE1 haplotypes responded to ramipril significantly faster than those who were heterozygotes, as measured by time to reach mean arterial pressure. Fan et al. [23] performed a similar study in a Chinese population consisting of 3408 untreated hypertensives. The report identifies a significant effect of the ACE2 variant rs2106809 in predicting diastolic blood pressure response to captopril in women. After a 4-week treatment period, those with the CC genotype achieved an adjusted mean diastolic blood pressure reduction 3.3 mm Hg greater than those with the CT and CC genotypes combined. A third study examined the adducin 2 (*ADD2*) gene, a positional candidate gene from the Family Blood Pressure Program that has been associated with blood pressure in the rat [24]. Using 1133 hypertensive subjects from the Genetic Epidemiology Network of Arteriopathy (GENOA) study, Kardia et al. [24] genotyped 11 SNPs within the *ADD2* gene and found significant associations with systolic blood pressure for eight SNPs in those who were never treated. Using cross-validation statistical methods, they further identified several significant gene-by-drug interactions. The authors suggested their results indicate that differences in mean blood pressure levels depend upon an individual's genotype and the drug class administered. For example, individuals in this study with the AT or TT genotype of rs1541582 had higher mean systolic blood pressures in the "no treatment," "diuretic," and "diuretic plus others" treatment groups; however, those with these same genotypes in the "β-blocker" group had lower systolic blood pressure levels [24]. Although all three studies have limitations and require replication in additional populations, they provide preliminary evidence for the role of pharmacogenetic effects in hypertension and encourage further research into this area.

Genome-Wide Association

Due to the technologic and analytic advances driven in large part by the Human Genome and International HapMap Projects, GWA studies incorporating up to millions of markers and thousands of individuals are now feasible. The dense typing of both SNPs and copy number variants (CNVs) throughout the genome, along with careful consideration of the established linkage disequilibrium patterns in different populations, should allow for the enhanced detection of disease genes and alleles contributing to complex traits, such as EH. Although a Japanese study successfully identified 19 essential hypertension loci using almost 19,000 microsatellite markers [25], this technique is much more widely applied using SNPs due to their relative ease and affordability of typing.

The first published GWA results for EH come from the Wellcome Trust Case-Control Consortium (WTCCC) using the Affymetrix (Santa Clara, CA) 500K chip, in which 14,000 cases among seven complex diseases, including hypertension (about 2000 cases), were compared with a shared control cohort of about 3000 individuals [26••]. Although hypertension was the only disease that did not identify genome-wide statistically significant variants, taking into account the number of SNPs and correcting for multiple testing, several genes of interest were identi-

fied by examining the most significantly associated SNPs ($P < 0.00001$). The strongest signal for blood pressure was found on chromosome 1. Using an expanded set of controls comprised of the cases from the other six disease sets, the strongest signal for hypertension was then detected on the X chromosome. A replication study is currently under way using Family Blood Pressure Program individuals. So far, only one of the six most significant *P* values has been replicated [27].

Similar results have been found in a study using the Affymetrix 100K chip to investigate the Framingham Heart Study families for association with systolic and diastolic blood pressure [28]. Again, no variant achieved genome-wide significance and researchers were not able to strongly replicate any previously identified associations.

Although these are only the first two GWA studies to be published, the results suggest that further refinement of the study design may be necessary to identify genes of interest for hypertension. The power of the WTCCC study was estimated at only 43% for alleles conferring a relative risk of 1.3, an effect size not unlikely to be observed in hypertension [26••]. As argued by the authors of the WTCCC paper, it may be that hypertension has fewer common alleles of larger effect than the other phenotypes in the report, in which case increasing sample size by combining multiple large-scale studies would help. Additionally, it may have happened that those susceptibility variants contributing to hypertension may have been poorly tagged by the set of variants on the 500K chip [26••], a problem that can be remedied by increasing the number of markers assayed, which is now possible with the availability of denser genotyping chips. It will be interesting to see the results from GWA studies using the densest set of variants available, one million SNPs, as their coverage of the genome is significantly greater than those chips used in either of the first two GWA studies. Finally, the WTCCC report also notes that detailed phenotyping was not performed on the control cohort, and because hypertension is one of the most prevalent diseases examined in their report, there is the possibility of misclassification bias impacting the findings for hypertension [26••]. Specifically screening controls to exclude those with increased blood pressure, as is generally done in studies of a single disease, alleviates this problem. Although neither of the first two GWA studies for EH demonstrated significant genome-wide findings, it appears likely that a combination of increasing sample size and the number of markers assayed will improve the chances of future studies identifying EH-associated alleles.

Rodent Models

The rat is an established rodent model for studying hypertension. Since the early 1960s, researchers have been selectively breeding rats to generate inbred hypertensive strains that closely mirror the human phenotype [29,30]. To date, 10 inbred strains of rat exist that display traits common to human essential hypertension, most of which are derived from the Wistar strain [31]. In addition to the several inbred strains, transgenic rats are now common [32], a basic genetic infrastructure has been developed [33,34], and a wealth of rat genetic information is available via the Rat Genome Database (http://www.rgd.mcw.edu/).

Although intercross linkage studies of rats have been a commonly used method of hypertension gene identification in rodents, the relatively recent development of several consomic and congenic strains of rats has enabled studies to narrow down large QTL regions and identify novel genomic regions related to blood pressure regulation. Consomic and congenic rats have been selectively backcrossed and bred to transfer a single chromosome (consomic) or a specific region within a chromosome (congenic) from one strain onto the background of a second strain. These strains have already been successfully used to identify several small regions of the rat genome linked to hypertension [35–37].

Most recently, a 2007 study by Moreno et al. [37] found several loci that appear to be protective against the development of hypertension in Dahl salt-sensitive (SS) rats. They previously found that substitution of chromosome 13 from the normotensive Brown Norway (BN) rat onto the genomic background of the SS hypertensive rat protected the new SS-BN^{13} rat from developing hypertension [38]. Through the generation of 23 overlapping congenic lines that covered chromosome 13, they were able to refine the possible location of the protective region(s) to four small areas of the chromosome [37]. The authors suggest that these regions may interact epistatically and that no region alone could protect from hypertension [37]. This complex interaction may explain some of the difficulties that have been encountered in identifying essential hypertension candidate genes.

In addition to in-depth physiologic studies of congenic and consomic strains, high-throughput expression profiling has also been recently used to identify new candidate genes from such strains. It is recognized that differential expression does not necessarily equate with difference in function, and the candidate genes identified through this method need further testing to ensure their validity [39].

A 2007 study by Clemitson et al. [40] used congenic strains to further explore the blood pressure QTL BP1 (Blood Pressure 1) that was initially found through a cross of the spontaneously hypertensive rat (SHR) and Wistar-Kyoto rat (WKY). Only one of the congenic strains that represented a 3-Mb segment of BP1 exhibited a blood pressure difference. Through expression profiling of SHR and WKY for genes within the new region, one gene, *Spon1*, was differentially expressed. This gene may have antiangiogenic properties and warrants further investigation.

A similar study by Graham et al. [41] used stroke-prone spontaneously hypertensive rats (SHRsp) and WKY congenics to examine a salt-sensitive hypertension QTL

on rat chromosome 2. One congenic strain showed a significantly lower salt-loaded systolic blood pressure when compared to the parental SHRsp strain, and an expression profile of whole kidneys showed *Edg1* and *Vcam1* to be differentially expressed. Reverse transcription polymerase chain reaction confirmed these findings.

Another use of congenic strains and expression profiling to investigate blood pressure QTLs was performed by Lee et al. [42]. Segments representing two blood pressure QTLs on chromosome 5, originally discovered in SS rats, were introduced from the Lewis rat onto a SS rat background to make congenic strains with one or both QTLs. Expression profiling was done using a custom chip that included all genes from both QTLs, and they found two differentially expressed genes, *Dmrta2* and *Nfia*. The expression of these genes changed depending on whether the strain had one or both Lewis segments, suggesting that some pathways of interaction exist. They further explained that these two genes are transcription factors involved in signaling pathways that could affect blood pressure. Much more needs to be done to verify the importance of these genes, but the initial results are promising.

Conclusions

For more than 15 years, the search for the underlying genetic etiology of human essential hypertension has provided a constant challenge. Early successes in identification of Mendelian forms of hypertension has given us clues to the basic genes and pathways involved in blood pressure regulation, but it has been difficult to verify the relative importance of these genes and mutations in the general population. Although linkage and association techniques are imperative in identifying candidate genes and susceptibility alleles, the results have often been inconsistent. However, this is most likely not due to inherent weaknesses of the methods used, but rather due to the ways in which they are applied. To identify the sequence variants underlying EH, investigators must recognize the need for extremely large sample sizes, as evidenced by the WTCCC GWA study using 3000 shared controls [26••], while working to refine the collection and in-depth standardized phenotyping of hypertensive and normotensive individuals.

The variable nature of blood pressure is well known and relying on three consecutive measurements to define hypertension status, although an integral part of a normal doctor's visit, is being revealed as less useful for genetic research. More care must be taken to improve precision and accuracy in phenotyping procedures, and to develop standardized conditions to reduce environmental noise, which is prevalent. Due to white-coat [43] and masked hypertension [44], techniques such as 24-hour ambulatory measurements may be necessary to fully understand the blood pressure profile of a single individual [45]. In addition, the examination of a wide variety of hypertension-related phenotypes, intermediate phenotypes, and blood pressure stress-response phenotypes will not only provide a dissected viewpoint of the disease, but will also increase understanding of the pathways involved in the phenotype as a whole. Finally, because collaborations and combining of samples will likely be required to achieve samples adequately powered to detect EH allelic effects, the standardization of phenotyping across studies is crucial and will present its own new challenges.

Although GWA studies hold promise in being able to identify genes and variants that may have been missed in previous linkage and association studies, this technique must be combined with suitably large, homogenous, well-phenotyped populations. With highest throughput SNP genotyping platforms now commercially available, and with recent advances in large-scale sequencing [46••], it seems that we may be able to directly interrogate much of the genome of hypertensive individuals. More GWA results for hypertension can be expected in the near future, as many of the established hypertensive populations with linkage data are now either being genotyped for GWA analysis or are currently in the analysis stages. Combining data from these populations offers one approach to increasing sample size and the likelihood of obtaining significant results.

Perhaps the most promising aspect of hypertension research is the ability to combine research to form a systems biology approach. Physiologic pathways and candidate genes can be identified by human studies and then tested in rats. Rats have the advantage of being in controlled environments with equally controlled genetic backgrounds. Physiologic testing in rats can lead to a better understanding of the genetic interactions found in human populations. Research collaborations can also work in the opposite fashion, with rat physiologic discoveries leading to further genetic studies in humans. In addition, the availability of hypertensive populations in which multiple techniques have been applied, including linkage, candidate gene association, GWA, and expression profiling, should allow for an integrated analytical framework for dissecting the genetics of EH. In summary, the sequence variants influencing the phenotype of EH have remained elusive, but with denser mapping techniques, better phenotyping methods, open collaborations, full utilization of animal models, and a systems biology approach, we should begin to discover those variants that can ultimately lead to its enhanced prevention, detection, and treatment.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hajjar I, Kotchen TA: **Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000** [see comment]. *JAMA* 2003, **290:**199–206.
2. Kearney PM, Whelton M, Reynolds K, et al.: **Worldwide prevalence of hypertension: a systematic review** [see comment]. *J Hypertens* 2004, **22:**11–19.
3. Kannel WB: **Elevated systolic blood pressure as a cardiovascular risk factor.** *Am J Cardiol* 2000, **85:**251–255.
4. Mosterd A, D'Agostino RB, Silbershatz H, et al.: **Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989** [see comment]. *N Engl J Med* 1999, **340:**1221–1227.
5. Abney M, McPeek MS, Ober C: **Broad and narrow heritabilities of quantitative traits in a founder population.** *Am J Hum Genet* 2001, **68:**1302–1307.
6. Gu C, Borecki I, Gagnon J, et al.: **Familial resemblance for resting blood pressure with particular reference to racial differences: preliminary analyses from the HERITAGE Family Study.** *Hum Biol* 1998, **70:**77–90.
7. Jee SH, Suh I, Won SY, et al.: **Familial correlation and heritability for cardiovascular risk factors.** *Yonsei Med J* 2002, **43:**160–164.
8. Knuiman MW, Divitini ML, Welborn TA, et al.: **Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors.** *Ann Epidemiol* 1996, **6:**188–194.
9. Hansson JH, Nelson-Williams C, Suzuki H, et al.: **Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome** [see comment]. *Nat Genet* 1995, **11:**76–82.
10. Hansson JH, Schild L, Lu Y, et al.: **A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity.** *Proc Natl Acad Sci U S A* 1995, **92:**11495–11499.
11. Lifton RP, Dluhy RG, Powers M, et al.: **A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension.** *Nature* 1992, **355:**262–265.
12. Mune T, Rogerson FM, Nikkila H, et al.: **Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase.** *Nat Genet* 1995, **10:**394–399.
13. Shimkets RA, Warnock DG, Bositis CM, et al.: **Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel.** *Cell* 1994, **79:**407–414.
14. Tamura H, Schild L, Enomoto N, et al.: **Liddle disease caused by a missense mutation of beta subunit of the epithelial sodium channel gene.** *J Clin Invest* 1996, **97:**1780–1784.
15. Lifton RP, Dluhy RG, Powers M, et al.: **Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase.** *Nat Genet* 1992, **2:**66–74.
16. Geller DS, Zhang JJ, Wisgerhof MV, et al.: **A novel form of human Mendelian hypertension featuring non-glucocorticoid remediable aldosteronism.** *J Clin Endocrinol Metab* 2008, **93:**3117–3123.
17. Kato N, Julier C: **Linkage mapping for hypertension susceptibility genes.** *Curr Hypertens Rep* 1999, **1:**15–24.
18. Tobin MD, Tomaszewski M, Braund PS, et al.: **Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population.** *Hypertension* 2008, **51:**1658–1664.
19.• Cheung VG, Spielman RS, Ewens KG, et al.: **Mapping determinants of human gene expression by regional and genome-wide association.** *Nature* 2005, **437:**1365–1369.

This study provides a comparison of linkage and association analysis in the same dataset and was one of the first studies to demonstrate the feasibility of using dense SNP maps to identify loci for complex diseases.

20. Kohara K, Tabara Y, Nakura J, et al.: **Identification of hypertension-susceptibility genes and pathways by a systemic multiple candidate gene approach: the millennium genome project for hypertension.** *Hypertens Res* 2008, **31:**203–212.
21.• Lynch AI, Boerwinkle E, Davis BR, et al.: **Pharmacogenetic association of the NPPA T2238C genetic variant with cardiovascular disease outcomes in patients with hypertension.** *JAMA* 2008, **299:**296–307.

This study provides an excellent example of the complexity and logistical demands required to test for pharmacogenetic associations and interactions. The findings provide preliminary evidence for the effect of gene variants on antihypertensive treatment in relation to blood pressure and CVD.

22. Bhatnagar V, O'Connor DT, Schork NJ, et al.: **Angiotensin-converting enzyme gene polymorphism predicts the time-course of blood pressure response to angiotensin converting enzyme inhibition in the AASK trial.** *J Hypertens* 2007, **25:**2082–2092.
23. Fan X, Wang Y, Sun K, et al.: **Polymorphisms of ACE2 gene are associated with essential hypertension and antihypertensive effects of Captopril in women.** *Clin Pharmacol Ther* 2007, **82:**187–196.
24. Kardia SL, Sun YV, Hamon SC, et al.: **Interactions between the adducin 2 gene and antihypertensive drug therapies in determining blood pressure in people with hypertension.** *BMC Med Gen* 2007, **8:**61.
25. Yatsu K, Mizuki N, Hirawa N, et al.: **High-resolution mapping for essential hypertension using microsatellite markers.** *Hypertension* 2007, **49:**446–452.
26.•• Wellcome Trust Case-Control Consortium: **Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.** *Nature* 2007, **447:**661–678.

This is one of the first genome-wide association studies examining hypertension. Results from this study may lead to the identification of novel hypertension-susceptibility alleles.

27. Ehret GB, Morrison AC, O'Connor AA, et al.: **Replication of the Wellcome Trust genome-wide association study of essential hypertension: the Family Blood Pressure Program.** *Eur J Hum Genet* 2008 (Epub ahead of print).
28. Levy D, Larson MG, Benjamin EJ, et al.: **Framingham Heart Study 100K Project: genome-wide associations for blood pressure and arterial stiffness.** *BMC Med Genet* 2007, **8(Suppl 1):**S3.
29. Dahl LK, Heine M, Tassinari L: **Role of genetic factors in susceptibility to experimental hypertension due to chronic excess salt ingestion.** *Nature* 1962, **194:**480–482.
30. Okamoto K, Tabei R, Fukushima M, et al.: **Further observations of the development of a strain of spontaneously hypertensive rats.** *Jpn Circ J* 1966, **30:**703–716.
31. Rapp JP: **Genetic analysis of inherited hypertension in the rat.** *Physiol Rev* 2000, **80:**135–172.
32. McBride MW, Graham D, Delles C, et al.: **Functional genomics in hypertension.** *Curr Opin Nephrol Hypertens* 2006, **15:**145–151.
33. Kwitek AE, Gullings-Handley J, Yu J, et al.: **High-density rat radiation hybrid maps containing over 24,000 SSLPs, genes, and ESTs provide a direct link to the rat genome sequence.** *Genome Res* 2004, **14:**750–757.
34. Steen RG, Kwitek-Black AE, Glenn C, et al.: **A high-density integrated genetic linkage and radiation hybrid map of the laboratory rat.** *Genome Res* 1999, **9:**AP1–AP8, insert.
35. Lee SJ, Liu J, Qi N, et al.: **Use of a panel of congenic strains to evaluate differentially expressed genes as candidate genes for blood pressure quantitative trait loci.** *Hypertens Res* 2003, **26:**75–87.

36. Cowley AW Jr, Liang M, Roman RJ, et al.: **Consomic rat model systems for physiological genomics.** *Acta Physiol Scand* 2004, **181:**585–592.
37. Moreno C, Kaldunski ML, Wang T, et al.: **Multiple blood pressure loci on rat chromosome 13 attenuate development of hypertension in the Dahl S hypertensive rat.** *Physiol Genomics* 2007, **31:**228–235.
38. Cowley AW Jr, Roman RJ, Kaldunski ML, et al.: **Brown Norway chromosome 13 confers protection from high salt to consomic Dahl S rat.** *Hypertension* 2001, **37(2 Part 2):**456–461.
39. Cowley AW Jr: **The genetic dissection of essential hypertension.** *Nat Rev Gen* 2006, **7:**829–840.
40. Clemitson JR, Dixon RJ, Haines S, et al.: **Genetic dissection of a blood pressure quantitative trait locus on rat chromosome 1 and gene expression analysis identifies SPON1 as a novel candidate hypertension gene.** *Circ Res* 2007, **100:**992–999.
41. Graham D, McBride MW, Gaasenbeek M, et al.: **Candidate genes that determine response to salt in the stroke-prone spontaneously hypertensive rat: congenic analysis.** *Hypertension* 2007, **50:**1134–1141.
42. Lee NH, Haas BJ, Letwin NE, et al.: **Cross-talk of expression quantitative trait loci within 2 interacting blood pressure quantitative trait loci.** *Hypertension* 2007, **50:**1126–1133.
43. Angeli F, Verdecchia P, Gattobigio R, et al.: **White-coat hypertension in adults.** *Blood Press Monit* 2005, **10:**301–305.
44. Papadopoulos DP, Makris TK: **Masked hypertension definition, impact, outcomes: a critical review.** *J Clin Hypertens (Greenwich)* 2007, **9:**956–963.
45. Verdecchia P, Angeli F, Gattobigio R, et al.: **The clinical significance of white-coat and masked hypertension.** *Blood Press Monit* 2007, **12:**387–389.
46.•• Wheeler DA, Srinivasan M, Egholm M, et al.: **The complete genome of an individual by massively parallel DNA sequencing.** *Nature* 2008, **452:**872–876.
This is the first report of sequencing an individual's entire genome using next-generation technologies. It has implications for the routine use of such technology in human disease genetics research, which will allow for the direct interrogation of an individual's full genome and may aid in hypertension disease-gene discovery.