Genetics of hypertension: discoveries from the bench to human populations

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Franceschini N, Le TH. Genetics of hypertension: discoveries from the bench to human populations. Am J Physiol Renal Physiol 306: F1–F11, 2014. First published October 16, 2013; doi:10.1152/ajprenal.00334.2013.—Hypertension is a complex trait that is influenced by both heritable and environmental factors. The search for genes accounting for the susceptibility to hypertension has driven parallel efforts in human research and in research using experimental animals in controlled environmental settings. Evidence from rodent models of genetic hypertension and human Mendelian forms of hypertension and hypotension have yielded mechanistic insights into the pathways that are perturbed in blood pressure homeostasis, most of which converge at the level of renal sodium reabsorption. However, the bridging of evidence from these very diverse approaches to identify mechanisms underlying hypertension susceptibility and the translation of these findings to human populations and public health remain a challenge. Furthermore, findings from genome-wide association studies still require functional validation in experimental models. In this review, we highlight results and implications from key studies in experimental and clinical hypertension to date.

Hypertension is a leading cause of renal and cardiovascular disease morbidity, mortality, and disability worldwide (48, 64, 67). Hypertension affects one in every three US adults (10, 39) with a disproportionate burden in US minorities, particularly African Americans (43). In most cases, the etiology of hypertension is unknown (essential hypertension). Blood pressure is an important predictor of health in populations. The American Heart Association Strategy Impact Goals to improve cardiovascular health to all Americans by 2020 include an ideal blood pressure target (<120/80 mmHg) among seven attributes for cardiovascular health (72), therefore recognizing the importance of blood pressure levels for population health.

Several mechanisms and pathways for blood pressure regulation have been described in studies of humans and experimental animal models (41, 42, 44, 51), and their dysfunction has been shown to lead to hypotensive and hypertensive disease states. However, the mechanisms contributing to blood pressure homeostasis in the general population are complex and are likely modulated by genetic factors and their interactions with environmental and behavioral factors. Studies of genetic determinants of blood pressure in humans and experimental animal models can provide complementary information on disease susceptibility. In this regard, gene-targeting studies in animals can clarify the biology and function of genes affecting blood pressure. Genetic studies in humans provide population-specific information on disease susceptibility for variants affecting blood pressure in the context of a diverse diet, physical activity, and other behavioral factors and can also inform on allelic heterogeneity and ancestry-specific genetic susceptibility (for example, ALDH2 variants in east Asians) (59). The difficult task remains in the bridging of evidence from controlled experimental data to translate the findings to human populations and public health. Conversely, recent genome-wide scans in humans have uncovered previously unsuspected genes for blood pressure that will need functional validation in experimental settings. This review aims to provide an update of the current knowledge of the genetics of hypertension by discussing 1) evidence from animal models, 2) evidence from human Mendelian disorders, and 3) evidence from population studies.

Genetic Models of Hypertension in Rodents: Role of the Kidney

Over 50 years ago, the research community developed rat models of hypertension by which to study essential hypertension in humans. Through selective breeding, several commonly employed rat models of genetic hypertension were generated: the spontaneously hypertensive rats (SHR), the Dahl salt-sensitive rats (DS), and the Milan hypertensive rats. Though these models represent only a rare form of human hypertension with a Mendelian mode of inheritance, studies using these inbred strains have generated key insights. In particular, kidney cross-transplantation studies using hypertensive and normotensive rats derived from one single strain overwhelmingly demonstrated that the genotype of the donor kidney plays a principal role in determining chronic blood pressure levels in the recipient (6, 20, 81, 89). Dahl and colleagues (20) concluded from these studies that “genetic factors operating through the kidney can chronically modify blood pressure”.

As blood pressure is a quantitative trait, much effort has been focused on the identification of genes underlying quantitative trait loci (QTLs) that influence blood pressure regulation.
The utilization of traditional crosses and linkage analysis for gene mapping in these hypertensive rat strains led the way for successful identification of numerous blood pressure QTLs on virtually every chromosome in the rat. Over 350 blood pressure QTLs across the rat genome have been reported to date (Rat Genome Database: http://rgd.mcw.edu/). Despite integrative approaches using congenic strategies for fine-mapping, gene expression arrays, and comparative and functional genomics, identification of causative gene(s) underlying a QTL has remained a significant challenge. Factors contributing to this bottleneck include small phenotypic effects of a causative gene and epistatic interactions of genes that influence blood pressure but with opposing effects.

There are, however, a few examples of successful gene identification that deserve particular mention since they provide mechanistic insights into the regulation of blood pressure. The first of these examples was linkage analysis in the Dahl rats that identified genetic polymorphisms in the 11β-hydroxylase gene (Cyp11b1) that cosegregated in a Mendelian manner with the adrenal capacity to synthesize 18-hydroxy-11-deoxy-corticosterone (18-OH-DOC) and blood pressure (17). Compared with the Dahl salt-sensitive strain and 11 other strains, the Dahl salt-resistant strain was found to have a different 11β-hydroxylase allele by restriction fragment length polymorphism and 5 amino acid substitutions in the 11β-hydroxylase protein that were associated with a reduced capacity to synthesize 18-OH-DOC (17). Through a series of studies using congenic strategy that resulted in the generation of a 177-kb congenic segment containing nine known genes, the Cyp11b1 gene is the only gene among the nine genes in this locus that has known biological functions related to blood pressure (38). Although earlier binding studies demonstrated that 18-OH-DOC has one-fiftieth binding affinity to mineralocorticoid receptors compared with aldosterone (30, 84), the mechanism by which the 11β-hydroxylase variants affect blood pressure can be explained by observations showing that circulating levels of 18-OH-DOC in the rat are much higher than that of aldosterone (84). Thus, at elevated levels, 18-OH-DOC can compete with aldosterone for binding to the mineralocorticoid receptors (84). While these studies may explain the blood pressure difference between the Dahl salt-sensitive and Dahl salt-resistant rats, other rat strains such as Lewis rats that carry the same 11β-hydroxylase allele as the Dahl salt-sensitive strain and 11 other strains, the SHR has been the most widely studied rat model of hypertension. Although multiple blood pressure QTLs have been identified in this model, it was not until efforts to map intermediate phenotypes of the metabolic syndrome in an SHR-derived strain that successful identification of a gene underlying a blood pressure QTL was achieved. In this regard, linkage studies of adipocyte insulin sensitivity and catecholamines (3), followed by a series of congenic fine-mapping strategies, gene expression analysis, and comparative genomics, resulted in the identification that a loss-of-function mutation in the gene that encodes the CD36 fatty acid transporter could explain these intermediate phenotypes of metabolic syndrome (84). The generation of multiple transgenic lines showed that expression of wild-type CD36 rescued the metabolic syndrome in the SHR (85) and led to the observation that differences in renal expression of CD36 could explain the differences in blood pressure between the transgenic line with lower blood pressure and those with high blood pressures (84, 86). Kidney cross-transplant studies later confirmed that the level of renal CD36 determines the level of blood pressure (84, 86). The mechanism by which renal expression of the CD36 fatty acid transporter influences blood pressure is not understood, and it remains to be determined whether it influences blood pressure in humans.

The identification that genetic variants in the genes encoding 11β-hydroxylase, α-adducin, and CD36 influence blood pressure in the rat models of genetic hypertension illustrates a mechanism that is consistent with the hypothesis set forth by Arthur Guyton and colleagues 40 years ago (42). They argued that the kidney, by regulating sodium excretion, plays a central role in hypertension (42). This notion is further reinforced by findings from studies in Mendelian forms of hypertension and hypotension in humans described below.

**Genetics of Mendelian Forms of Hypertension and Hypotension in Humans: Role of the Kidney**

Much of our understanding of genetic mechanisms of blood pressure regulation in humans has resulted from investigations of rare Mendelian forms of hypertension and hypotension. In this regard, Lifton and others have identified over 20 genes with mutations with large effects on blood pressure. These genes primarily encode sodium transporters or channels in the kidney, or components belonging to the mineralocorticoid pathway that ultimately influences the activity of the mineralocorticoid receptor which regulates the epithelial sodium channel activity, thereby affecting renal salt reabsorption (the reader is referred to Refs. 22 and 70 for an extensive review of these genes). As mentioned above, mutation in the Cyp11b1 gene resulting in decreased enzymatic capacity to synthesize 18-OH-DOC is thought to afford protection for the Dahl...
salt-resistant rat from salt-induced hypertension. In humans, loss of regulatory control mutation resulting from chimeric gene duplication due to unequal crossing over between the two closely linked aldosterone synthase and 11β-hydroxylase genes is attributable to the rare syndrome of glucocorticoid-remediable aldosteronism. In this instance, the aldosterone synthase activity is no longer under the control of angiotensin II but is controlled by the regulatory region of 11β-hydroxylase that is regulated by adrenocorticotropic hormone (ACTH) (68, 69). More recently, mutations in the WNK (with no K-lysine) serine-threonine kinases WNK1 and WNK4 were demonstrated to cause pseudohypoaldosteronism type II disorder of hypertension (100), due to alteration in their coordinated actions to regulate the transport of sodium, chloride, and potassium in the distal nephron (57). Taken together, evidence from rat models of genetic hypertension and human monogenic forms of hypertension illustrate that the kidney, by regulating sodium balance, plays a key role in blood pressure regulation. A logical question follows whether this paradigm holds true in human essential hypertension.

**Genetics of Hypertension and Blood Pressure in Human Populations**

Blood pressure has a substantial heritable component (30–50%) in humans, as illustrated by familial aggregation of hypertension and the highly penetrant genetic variants causing monogenic forms of hypertension and hypertension mentioned above. To address genetic causes of hypertension in the general population, earlier studies included association analyses of candidate genes belonging to biological or physiological pathways known to affect blood pressure. In particular, genes encoding components of the renin-angiotensin system have been analyzed as candidate genes for inherited forms of hypertension in humans. For example, the M235T variant of the human angiotensinogen gene (AGT) has been shown to be linked to hypertension and associated with a modestly elevated plasma angiotensinogen concentration in human hypertensive siblings (53). Although amino acid 235 is in a nonconserved portion of the angiotensinogen protein and variation of this amino acid does not affect protein stability, the M235T variant was later found to be in linkage disequilibrium (LD) with a single nucleotide substitution variant in the promoter of the AGT gene that was associated with increased transcriptional activity of the gene (50). Patients carrying the variant allele were demonstrated to have increased levels of AGT mRNA (50).

To provide direct proof of a causal relationship that mutations in the angiotensinogen gene that increase circulating plasma levels of angiotensinogen could directly increase blood pressure, Kim and Smithies (95) used a targeted gene duplication and deletion approach to generate mouse lines with one to four functional copies of the Agt gene (61). Through this gene titration approach, they demonstrated a positive correlation between plasma angiotensinogen levels and the number of Agt gene copies, as well as a direct linear relationship between blood pressures and number of copies of Agt genes (61). Despite the biological plausibility, the finding in a small cohort of hypertensive siblings and the proof of concept in the mice, the effect of the AGT M235T variant on blood pressure was not duplicated in some human populations (26, 76).

Similarly, inconsistencies have been seen in association studies of the insertion/deletion polymorphism of the angiotensin-convert enzyme (ACE) gene that correlates with circulating plasma ACE levels (21, 40, 54, 70). The Gstm1 gene is also an example of challenges in translating findings from experimental models to human hypertension. Gstm1, a member of the glutathione-S-transferase superfamily of genes, was identified as a strong positional and functional candidate gene for hypertension in the stroke-prone spontaneously hypertensive rat (SHRSP) (52). Decreased expression of the GSTM1 enzyme along with an associated increase in oxidative stress have been demonstrated in the kidneys of SHRSP rats (75). Reduction in GSTM1 levels in vascular smooth muscle cells in vitro causes increased production of reactive oxygen species and cell proliferation (102). Although the common deletion variant of GSTM1 was found to be associated with end-organ damage such as accelerated kidney disease progression in hypertension-associated kidney disease (14) and end-stage renal disease (2) in different human cohorts, it has not been demonstrated to be associated with hypertension in humans (23). Multiple other candidate genes analyses, as well as studies using family-based, genome-wide linkage analysis for hypertension have shown inconsistent results (8, 47, 92).

Recent discovery efforts have used hypothesis-free genome-wide association scans (GWAS) to identify genomic loci for blood pressure variation and hypertension susceptibility. These studies have been successful in identifying common genetic variants (allele frequency >5%) for complex diseases including blood pressure traits (28). Additional complementary methods used for gene discovery in individuals with recent admixture, such as African Americans, are admixture mapping analyses, which are based on alleles that differ in frequency across populations of different ancestry and are thus suitable to the study of diseases, such as hypertension, with disparities among racial/ethnic groups (24, 103). Findings for blood pressure traits using GWAS and admixture mapping analyses in populations studies are described below.

**Overview of genome-wide methods to study genetic determinants in humans.** GWAS use dense sets of genetic markers (500,000 to 1 million) to investigate associations of single nucleotide polymorphism (SNP) with complex traits. GWA studies are usually powered for common variants, which are defined as having the minor allele frequency of at least 5% in a population. To increase sample size for variant discovery, data are combined across studies using meta-analyses. Additional SNPs are imputed using reference panels of ancestry-specific populations from the International HapMap Project (34) or the 1,000 Genomes Project (1). For populations with admixture (e.g., Hispanics, African Americans) and/or not represented in the HapMap samples (American Indians), a strategy to improve imputation quality is to obtain study-specific reference haplotypes by using genotype data from a subset of individuals (for example, a sample of individuals chosen to be representative of individuals in the study have dense genotyping, which is then used to estimate haplotypes for imputation in the remaining individuals in the study) (71). The associations rely on the LD or correlation of typed (or imputed) SNPs with unknown functional variants. Therefore, SNPs identified in GWAS are usually proxies of untyped functional variants, which has implications for fine-mapping of genomic regions (5). Population stratification can lead to spu-
rious associations at markers that have different allele frequency among ancestry subpopulations, such as alleles that are more common among African Americans than European ancestry individuals. In other words, the observed differences in allele frequencies between the cases and controls are due to systematic differences in ancestry rather than association of genes with disease (35). Adjustments for population stratification are usually done using principal components and other methods (87).

To adjust for multiple testing and to decrease false-positive rates (type I error), stringent P values are used (usually 5.0 \times 10^{-8} for GWAS). For variants reaching the P value threshold, further validation is required by replication of the associations in additional individuals for the same trait (15). Consortia and collaborative studies have enabled meta-analyses of multiple GWAS based on large samples and statistical power sufficient to identify novel common variants. The National Human Genome Research Institute (NHGRI) has an ongoing repository of all published SNP-trait associations with 10^6 alleles (36). Additional studies have confirmed the presence of additional variants to be discovered that may actually be used advantageously for gene discovery. For example, some variants may have a higher allele frequency or a larger effect size in some populations, which would increase the power to identify the associations (59). The Asian Genetic Epidemiology Network BP (AGEN-BP) work group recently published its blood pressure GWAS (59). Using a much smaller discovery sample compared with European ancestry ICBP (19,608 East Asian individuals) and a two-stage replication in up to 30,000 additional East Asians, they identified four novel loci and a variant near the NTR3 locus, previously described in ICBP for European ancestry individuals (28, 59).

When the associations at 13 loci in East Asians and individuals of European ancestry are compared, differences in allele frequency and in the magnitude of effect estimates affected the P values and sample size required to reach significance. For example, the CASZ1 SNP rs880315 (at-risk C allele frequency 0.59 in East Asians and 0.35 in Europeans) that did not reach genome-wide significant levels in Europeans but was found to show a significant association with blood pressure in the AGEN-BP meta-analysis (59). The study also identified a novel blood pressure SNP at the TBR3 locus, demonstrating the presence of allelic heterogeneity at this locus (28, 59, 65).

Additional blood pressure studies have been recently published for a total of ~50 common genetic variants associated with blood pressure or hypertension through GWAS or admixture mapping (28, 32, 46, 56, 65, 77, 79, 83, 101, 103). These studies include GWAS using gene-centric arrays (37, 56), and studies of individuals of diverse ancestry including African Americans (32, 33, 103) and Asians (16).

Several of the blood pressure-associated regions identified through GWAS extend over multiple genes due to the strong LD or local correlation between SNPs in individuals of European ancestry. Studying populations with less SNP correlation may thus facilitate finding causal gene(s) in these loci, i.e., fine-mapping genomic regions. In the Genetic Epidemiology NeTwork of Blood Pressure (COGENT-BP) consortium, a large GWAS meta-analyses of blood pressure of 29,378 individuals of African ancestry from 19 discovery cohorts, we were able to fine map four known loci by reducing the length of the genomic region of associations (EBF1, ATP2B1, NT5C2, and ULK4) (33).

Several collaborative efforts to study blood pressure traits in non-European ancestry individuals have been established and are expected to yield novel findings in the coming months. These consortia include the Japanese Millennium Genome Project, the Korea Association Resource consortium, the Asian Genetic Epidemiology Network, the NHLBI Candidate-Gene Association Resource (African Americans), the COGENT-BP (African and African Americans), and the Genomics of Blood Pressure for Hispanics Consortium (GHPB, US and Mexican Hispanics). Loci identified may provide new insights into the biology of blood pressure regulation and may reveal targets for therapy and for population-level risk reduction.
Population-specific and rare/low-frequency variants. In addition to allelic heterogeneity, both population-specific variants and variants with effects across ancestries (cosmopolitan ones) may contribute to hypertension risk. The AGEN-BP GWAS described an association at the ALDH2 locus for a SNP in LD with rs671, a variant previously associated with hypertension mediated by alcohol consumption in Asians (59). The rs671 variant is common in East Asians (MAF 5%) but not poly-morphic in Europeans, and is an example of a population-specific common variant influencing the blood pressure trait. Population specificity becomes even more important for low-frequency and rare variants (11).

The small proportion of the variance in quantitative, blood pressure-related traits explained by common SNPs in GWAS (11), and recent high-throughput, commercial exome genotyping arrays which have predominantly common variants have become affordable for use in population-based whole exome sequencing. Current high-throughput, commercial exome genotyping arrays which have predominantly common variants have been used to detect rare, highly penetrant and novel alleles in genes underlying monogenic disorders (4, 13, 80) and some complex diseases (49). For example, exome sequencing revealed that partial or total loss-of-function rare variants of MTNR1B contribute to type 2 diabetes risk (9). More recently, in an effort to identify genes underlying the complex cardiovascular disease traits, the NHLBI Exome Sequencing Project (ESP) has selected individuals from the extremes of the blood pressure distribution for whole exome sequencing. Current high-throughput, commercial exome genotyping arrays which have predominantly common variants have become affordable for use in population-based

Table 1. Genes near loci identified in GWAS associated with blood pressure and/or hypertension and their biological relevance in human and animal studies

<table>
<thead>
<tr>
<th>Gene (Name)*/Reference(s)</th>
<th>Mechanism(s)</th>
<th>Human Evidence</th>
<th>Animal Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17A1 (cytochrome P-450 enzyme) (66, 78)</td>
<td>Pathways of steroid synthesis</td>
<td>Congenital adrenal hyperplasia (MIM no. 202110)</td>
<td>Protein found in human pheochromocytoma</td>
</tr>
<tr>
<td>ADM (adrenomedullin) (28, 97)</td>
<td>Vasodilation and angiogenesis promotion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPPA/NPPB (natriuretic peptide A and B) (77)</td>
<td>Precursors for atrial- and B-type natriuretic peptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPR3 (natriuretic peptide clearance receptor) (28, 59, 97)</td>
<td>Natriuretic pathways</td>
<td></td>
<td></td>
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<tr>
<td>GUCA1A3-GUCY1B3 ($\alpha$- and $\beta$-subunits of soluble guanylate cyclase) (28, 97)</td>
<td>Both units form the guanylate cyclase enzyme that activates nitric oxide. Vasodilatory mechanism for nitrovasodilator drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDN3 (endothelin 3) (65, 97)</td>
<td>Potent vasoconstrictor</td>
<td></td>
<td></td>
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<tr>
<td>SLC4A7 (electroneutral sodium bicarbonate cotransporter) (28, 97)</td>
<td>Kidney sodium-bicarbonate cotransporter</td>
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<tr>
<td>PLCE1 (phospholipase C-epsilon-1 isoform) (28)</td>
<td>Potent vasoconstrictor</td>
<td></td>
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<tr>
<td>NPR3 (natriuretic peptide clearance receptor) (28, 59, 97)</td>
<td>Potent vasoconstrictor</td>
<td></td>
<td></td>
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<tr>
<td>HFE (hemochromatosis) (28, 97)</td>
<td>Potent vasoconstrictor</td>
<td></td>
<td></td>
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<tr>
<td>SLC3A9 (solute carrier family 39, zinc transporter) (28, 97)</td>
<td>Ion transport (cadmium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENPEP (glutamyl aminopeptidase amineopeptidase A) (59)</td>
<td>Ion transport (cadmium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP2B1 (ATPase, Ca2+ transporting, plasma membrane 1) (16, 59, 65, 96)</td>
<td>Ion transport (cadmium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS3 (nitric oxide synthase 3 (endothelial cell) (91)</td>
<td>Vasodilatory effects</td>
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<tr>
<td>PIK3CG (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma) (97)</td>
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<td></td>
</tr>
<tr>
<td>NOV (nephroblastoma overexpressed) (28, 94)</td>
<td>Angiogenesis, proliferation and inhibition of vascular smooth muscle cell growth and migration (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRB1 (adrenoceptor beta 1) (97)</td>
<td>Mediates physiological effects of the hormone epinephrine and the neurotransmitter norepinephrine</td>
<td>Associated with resting heart rate in humans (88)</td>
<td></td>
</tr>
</tbody>
</table>

VSMC, vascular smooth muscle cells; SBP, systolic blood pressure. *Listed genes are from genome-wide association scans (GWAS) studies.
studies and can be supplemented by the addition of population-specific and low-frequency variants identified through sequencing.

More recent population studies using fine-mapping genotyping or sequencing of blood pressure candidate genes have identified common and rare variants accounting for blood pressure distribution. For example, common variants in the NPPA and NPPB genes were associated with natriuretic peptide concentrations and found to contribute to interindividual blood pressure variation and hypertension risk (79). In a novel approach, known and predicted functional mutations in the genes responsible for the rare Mendelian hypertensive disorders due to renal salt wasting, i.e., Gitelman’s syndrome [SLC12A3 (NCCT)] and Bartter’s syndrome [SLC12A1 (NKCC2) and KCNJ1 (ROMK)] were identified through direct sequencing of 2,492 participants of the Framingham Heart Study (FHS) (55). Heterozygote carriers of these mutations were demonstrated to have clinically significant lower blood pressure and were protected from the development of hypertension compared with noncarriers (55). At least 1 in 64 FHS participants are carriers of a functional mutation of one of the three genes, explaining ~1% of blood pressure variation in the FHS population (55), larger than the fraction contributed by the more common variants identified in GWAS mentioned above. Future sequencing studies targeting genes with known function in blood pressure regulation in animal models and in monogenic disorders of hypotension and hypertension in humans may prove useful for discovery of both common and rare variants that can explain even a larger fraction of blood pressure variation in the general population.

Developments on the Horizon

Future research using approaches that leverage functional and biological information may further help in understanding the pathophysiology of complex traits such as hypertension. For example, the ENCODE (Encyclopedia of DNA Elements) Project has mapped and characterized a variety of functional elements including promoters, enhancers, repressor or silencer sequences, transcription factor binding sites, methylation sites, DNase I hypersensitive sites, and chromatin modifications in several cell lines including vascular endothelial cells (27). Pathway analysis can identify enriched pathways in a GWAS set and prioritize regions or candidate genes in genetic studies (98). Additional resources such as metabolomics could be set and prioritize regions or candidate genes in genetic studies. Pathway analysis can identify enriched pathways in a GWAS dataset and can be supplemented by population-scale sequencing. Nature 467: 1061–1073, 2010.


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GENES INFLUENCING BLOOD PRESSURE

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Review

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