Clinical and Experimental Hypertension

ISSN: 1064-1963 (Print) 1525-6006 (Online) Journal homepage: http://www.tandfonline.com/loi/iceh20

Molecular genetics of essential hypertension

M. Singh, A.K. Singh, P. Pandey, S. Chandra, K.A. Singh & I.S. Gambhir

To cite this article: M. Singh, A.K. Singh, P. Pandey, S. Chandra, K.A. Singh & I.S. Gambhir (2016): Molecular genetics of essential hypertension, Clinical and Experimental Hypertension, DOI: 10.3109/10641963.2015.1116543

To link to this article: http://dx.doi.org/10.3109/10641963.2015.1116543

Published online: 30 Mar 2016.

CLINICAL AND EXPERIMENTAL HYPERTENSION
http://dx.doi.org/10.3109/10641963.2015.1116543

Taylor & Francis
Taylor & Francis Group

Molecular genetics of essential hypertension

M. Singh[a], A.K. Singh[b], P. Pandey[a], S. Chandra[c], K.A. Singh[d], and I.S. Gambhir[a]

[a]Department of Medicine, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India,; [b]Department of Surgical Oncology, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India; [c]Department of Nephrology, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India; [d]Department of Pharmaceutics, Indian Institute of Technology, Banaras Hindu University, Varanasi, India

ABSTRACT

Hypertension is a major public health problem in the developing as well as in developed countries due to its high prevalence and its association with coronary heart disease, renal disease, stroke, peripheral vascular disease, and related disorders. Essential hypertension (EH) is the most common diagnosis in this disease, suggesting that a monocausal etiology has not been identified. However, a number of risk factors associated with EH have also been identified such as age, sex, demographic, environmental, genetic, and vascular factors. Recent advances in molecular biological research had achieved clarifying the molecular basis of Mendelian hypertensive disorders. Molecular genetic studies have now identified mutations in several genes that cause Mendelian forms of hypertension in humans. However, none of the single genetic variants has emerged from linkage or association analyses as consistently related to the blood pressure level in every sample and in all populations. Besides, a number of polymorphisms in candidate genes have been associated with differences in blood pressure. The most prominent candidate has been the polymorphisms in the renin–angiotensin–aldosterone system. In total, EH is likely to be a polygenic disorder that results from inheritance of a number of susceptibility genes and involves multiple environmental determinants. These determinants complicate the study of blood pressure variations in the general population. The complex nature of the hypertension phenotype makes large-scale studies indispensable, when screening of familial and genetic factors was intended. In this review, recent genetic studies exploring the molecular basis of EH, including different molecular pathways, are highlighted.

ARTICLE HISTORY
Received 23 June 2015
Revised 4 October 2015
Accepted 19 October 2015
Published online
15 March 2016

KEYWORDS
Association analysis; candidate gene; genetics; hypertension; linkage analysis

Introduction

Cardiovascular disease accounts for approximately 17 million deaths annually worldwide, almost one third of the total, out of these 9.4 million deaths due to complications of hypertension (1). Hypertension is a common, adjustable risk factor for coronary artery and cerebrovascular diseases which are major causes of morbidity and mortality. Hypertension is responsible for nearly 45% of deaths due to heart disease, and 51% of deaths due to stroke. Hypertension affects almost one third of the adult population worldwide and is associated with stroke and cardiovascular diseases, which are major causes of global health burden (2). Since the disease etiology is unknown in most cases, patients are classified as having "essential hypertension" (3).

Essential hypertension (EH) is a multifactorial disease, and a number of risk factors associated with hypertension including age, sex, family history of hypertension, demographic factors, overweight, diabetes mellitus, physical inactivity, smoking, excess consumption of sodium, coffee, and alcohol (4,5). These risk factors can be divided into two major groups: factors that are not modifiable, such as age, sex, ethnicity, and genetic factors; and factors that could be modified and may diminish or even prevent hypertension. Many clinical trials have shown that a lower level of blood pressure minimizes the prevalence of stroke and myocardial infarction (6). Hypertension is subjected to the risk for future cardiovascular events (7).

Population-based studies have reported that hypertension occurs in families in a Mendelian inheritance manner and can be seen in about 20% of families and varies around 60% in twin studies (8). Advancement in molecular biology research led to clearing up of some pathophysiologic pathways. The recently available human genome sequencing project has focused attention on the potential for genetic information that can benefit the diagnosis, evaluation, and treatment of hypertension (9). Recent advances have been achieved in clarifying the molecular basis of Mendelian hypertensive disorders (10). Causative genes and chromosomal fragments harboring disease susceptibility genes have been identified for glucocorticoid-remediable aldosteronism (11), Liddle's syndrome (12,13), mineralocorticoid excess (14) among others. Although, the genes themselves have not yet been identified, the genetic loci have been mapped, as in Gordon's syndrome (15), and in a pedigree affected with hypertension and brachydactyly (16).

Extensive efforts have also been made to identify the genes responsible for the development of EH. The task is

CONTACT Professor Indrajeet Singh Gambhir iac2k10@gmail.com Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India.

enormously difficult for several reasons. The inheritance of hypertension is low (only about 30% of blood pressure variance is attributable to genetic factors). On the other hand, extensive efforts have been made to search for causes of EH, most of the results were indecisive. A number of explanations were proposed for the difficulties in detecting susceptibility genes for EH (17). Nothing is known about the number of genes implicated, their mode of transmission, their quantitative effect on blood pressure, their interaction with other genes, or their modulation by environmental factors.

EH is a polygenic disorder that resulted from inheritance of a number of susceptibility genes and involves several environmental determinants. These determinants complicate the study of blood pressure variations in general population. The common approaches of chromosomal linkage mapping in affected families and further in identification of candidate genes has so far not been doing well for heritable diseases that involve multiple genes and their interactions and also the gene-environment interactions (18). Even though many research efforts have been made, the definite causes of EH remains partly understood. So it may be that blood pressure is dependent on a mosaic of many loci, each with a small influence or with a contribution at variance according to sex (19), age, race (20), or lifestyle (8).

General strategies to investigate the genetic basis of hypertension

To elucidate the genetic basis of EH, two major strategies are being used (i) association study and (ii) linkage analysis. These strategies are not equally exclusive, but can be combined into a single analytical method, such as the transmission/disequilibrium test (TDT) (21). Each of them has advantages and disadvantages depending on the situations tested. An association study, i.e., case-control study (which tests for different allele or genotype frequencies between case and control populations) allows the use of unrelated individuals; it is easier to collect a large set of samples using this concept than using a pedigree-based linkage analysis. Usually, a case-control study has greater statistical power than a linkage analysis, but it may also be responsible for increases in false positive results.

Human hypertension loci were mapped by a number of linkage analysis studies (22–27). In these cases, linkage analysis uses related individuals with members having marked hypertension, to examine the co-inheritance with hypertension of widely distributed markers in order to understand the genomic regions contributing to hypertension. By contrast, the genome-wide association studies (GWAS) examine unrelated individuals in a population, not related individuals, using genotypes of a large number of polymorphic markers in subjects with marked hypertension compared with healthy controls. The common strategy of linkage mapping in affected families to identify chromosomal loci from which candidate genes and genotypes are selected has not achieved similar successful for hypertension, because high blood pressure involves multiple genes and gene-environment interactions. A single nucleotide polymorphism (SNP) array raises the possibility that these SNPs could be used as markers in genome-wide association mapping studies, to identify hypertension susceptibility loci. SNPs are stable, di-allelic, the two alleles representing the "wild-type" and the variant form (18).

Association studies are adequate for testing candidate genes, or narrowing down to a particular gene once the α region of linkage has been detected. Four main strategies have been used to examine the linkage of genes or chromosome regions to hypertension, depending on the method used to select the loci to be tested, and the type of families to be studied as shown in Table 1 (28):

(1) Studies of Mendelian forms of hypertension
(2) Testing of candidate genes chosen on the basis of their known biochemical or physiologic function;
(3) Investigation of chromosome regions homologous to those that segregate with blood pressure in animal models, or regions harboring particular genes that shows linkage in animal models
(4) Systematic genome-wide searches for linkage (or linkage disequilibrium)

Mendelian forms of hypertension

Identification of genes involved in monogenic hypertension is comparatively easier to map than those in a multifactorial form of the disease. The investigation of heritable susceptibility to disease is an effort to correlate the disease phenotype with the underlying genotype. Such genotype–phenotype associations have been established for a large number of monogenetic disorders. The investigation of rare Mendelian

Table 1. General strategies to investigate genetic basis of hypertension [from (28)].

1. Studies of Mendelian forms of hypertension (mutated genes listed in the right side of the arrows)	
Glucocorticoid-remediable aldosteronism (GRA)	aldosterone synthase (*CYP11B2*) gene
11β-hydoxylase deficiency	11β-hydroxylase (*CYP11B1*) gene
Syndrome of apparent mineralocorticoid excess (AME)	11β-hydroxysteroid dehydrogenase kidney-type (*HSD11B2*) gene
Hypertension exacerbated by pregnancy	mineralocorticoid receptor (*MR*) gene
Liddle's syndrome	B and γ subunits of the epithelial sodium channel (*ENaC*) gene
2. Candidate genes chosen on the basis of known biochemical or physiological function	
1) Renin–angiotensin system	
Angiotensinogen (*AGT*), renin (*Ren*), angiotensin converting enzyme (*ACE*), angiotensin II type 1 and type 2 receptors	
2) Sympathetic nervous system	
β_1 and β_2 adrenergic receptors	
3) Ion transports	
G-protein β_3 subunit (*GNB3*)	
4) Others	
Vasoactive peptides, e.g., eNOS, ANP, and ADM	
Components involved in insulin resistance or metabolic function, e.g., lipoproteins	
3. Positional candidate genes (mostly) in chromosome regions implied by genome-wide screens	
Chromosome 3:	Angiotensin II type 1 receptor
Chromosome 5:	β_2 adrenergic receptor
Chromosome 8:	lipoprotein lipase
Chromosome 17:	ACE

forms of blood pressure variation, in which mutations in single genes have been detected, which impair renal salt handling, provides a molecular basis for understanding the pathogenesis of hypertension.

Several rare syndromes associated with hypertension are influenced by one or more mutations, whereby most of the causative genes identified for Mendelian forms of hypertension have turned out to be involved in the renin–angiotensin system or its components (Figure 1). These findings support the possible etiologic significance of the renin–angiotensin system in hypertension (28).

The rare Mendelian forms, where mutations in single genes cause variations in blood pressure, provided a molecular basis for understanding the pathogenesis of hypertension. Now mutations in eight genes that cause Mendelian forms of hypertension and nine genes that cause Mendelian forms of hypotension in humans have been recognized (29). These genes typically report very large effects on blood pressure (Table 2). Given the diversity of physiological systems that affect blood pressure, it is surprising that the mutated gene products in all cases act in the same physiological pathway in the kidney, altering net renal salt reabsorption (29). Mutations that increase sodium reabsorption and cause hypertension include mutations in the mineralocorticoid receptor (hypertension exacerbated by pregnancy) (30), aldosterone synthase (glucocorticoid-remediable aldosteronism), other enzymes synthesizing steroids that activate the mineralocorticoid receptor (11β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 11β-hydroxylase), the β- and γ-subunits of the renal epithelial sodium channel (Liddle's syndrome), and the serine-threonine kinases (WNK1 and WNK4 in pseudohypoaldosteronism type 2). Loss-of-function mutations were found to impair renal sodium reabsorption thus causing hypotension. They include genes encoding the mineralocorticoid receptor (autosomal dominant pseudohypoaldosteronism type 1), aldosterone synthase, 21-hydroxylase, the β- and γ-subunits of the epithelial sodium channel (EnaC; recessive pseudohypoaldosteronism type 1), the ATP-sensitive potassium channel ROMK (Bartter's syndrome type 2), and chloride channel CLC-NKB (Bartter's syndrome type 3). Different mutations, often in the same gene, may cause hyper or hypotension (9). However, monogenic disorders of blood pressure regulations are rare and do not explain blood pressure variability in the population at large (31). Nevertheless, these rare single gene mutations are still of importance because they give insight into biochemical, physiological and anatomic pathways through which common genetic variations may influence blood pressure (32–35).

However, no single genetic variant has emerged from linkage or association analyses as consistently related to an elevated blood pressure level in every sample and in all populations.

Candidate genes chosen on the basis of their known biochemical or physiological function

In the renin–angiotensin–aldosterone system, various candidate gene polymorphisms are responsible, which have their known biochemical or physiological function for blood

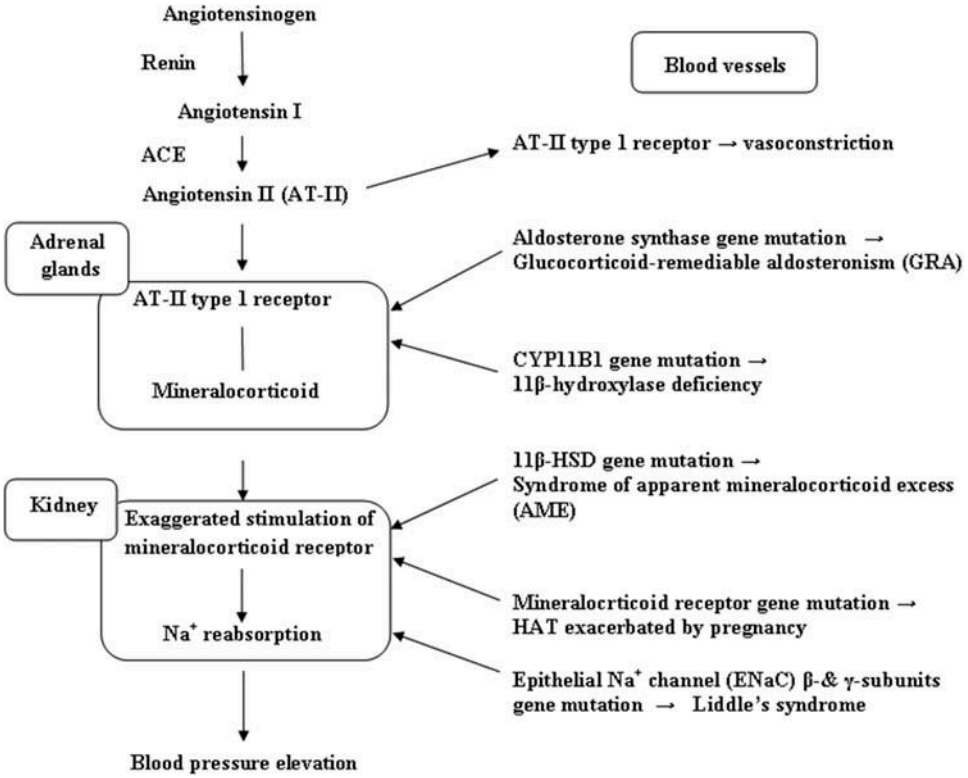

Figure 1. Schematic representation of genes identified for monogenic hypertension [from (28)].

Table 2. Mendelian forms of human hypertension [from (8, 32)].

Disease	Mutation	Effect on blood pressure
Glucocorticoid-remediable aldosteronism	Duplication of genes encoding aldosterone synthase and 11β-hydroxylase	Increased
synthase deficiency	Mutations in the gene encoding aldosterone synthase	Decreased
21-Hydrolase deficiency	Mutations in the gene encoding 21-hydroxylase	Decreased
Apparent mineralocorticoid excess	Mutations in the gene encoding 11β-hydroxylase	Increased
Hypertension exacerbated by pregnancy	Mutations in the ligand-binding domain of the mineralocorticoid receptor	Increased
Pseudohypoaldosteronism type 1 (autosomal dominant)	Loss-of-function mutations in mineralocorticoid receptor	Decreased
Pseudohypoaldosteronism type 2 (Gordon's syndrome)	Mutation is WNK kinase 1 and 4 encoding genes, Mutations in at least one of three genes mapped to 1q31–42, 12p13 and 17p11–q21	Increased
Hypertension with brachydactyly	Mutations mapped to 12p11.2–12.2	Increased
Peroxisome proliferator-activated receptor γ	Missense mutation	Increased
Liddle's syndrome	Mutations in the ENaC*β- or γ-subunit	Increased
Pseudohypoaldosteronism type 1 (autosomal recessive)	Loss-of-function mutations in ENaC subunits	Decreased
Pheochromocytoma syndromes	Mutation on RET gene on chromosome 10, VHL gene on chromosome 3, NF1 gene on chromosome 17	Increased
Gitelman's syndrome	Loss-of-function mutations in the NaCl cotransporter of the distal convoluted tubule	Normal or decreased
Bartter's syndrome	Loss-of-function mutations in genes required for salt reabsorption in the thick ascending loop of Henle	Normal or decreased

* ENaC: epithelial sodium channel

pressure regulation viz. angiotensinogen (AGT) (36), rennin, angiotensin-converting enzyme (ACE) (37), angiotensin (AT) II receptor (type 1) (38), and aldosterone synthase (11,39). The end product of this cascade, AT II, may enhance renal tubular sodium reabsorption by stimulating the aldosterone synthesis and release.

The angiotensinogen gene

The angiotensinogen (AGT) gene located on chromosomal 1q42.2 contains five exons and four introns having ~12Kb size (12 068 bases), which belongs to serpin gene superfamily and expressed in liver, brain, heart, adipose tissue, vessel walls, and kidneys. The Human AGT cDNA was 1455 nucleotides long and codes for a 485 amino acid long globular protein (~53.2 KDa) called angiotensinogen that acts as the sole substrate for renin (40) to produce angiotensin I in response to lower blood pressure. Expression of AGT is controlled by the 1.6 kb promoter region. The AGT gene has been an attractive candidate gene for hypertension (41). A linkage of the AGT gene to hypertension was reported early by Jeunemaitre et al. in 1992 (42). Caulfield reported the linkage of angiotensinogen locus in EH in white European families from the United Kingdom and African Caribbean's with an interesting observation that obese hypertensive individuals constitute a distinct genetic group of hypertensive individuals (43,44).

Jeunemaitre recognized 15 molecular variants and used them in case-controlled studies to test for association with hypertension (45). Among these polymorphisms, one encoding threonine instead of methionine at position 235 (M235T) and one encoding methionine instead of threonine at position 174 (T174M) in the gene product were associated with hypertension and plasma angiotensinogen levels in white Europeans and Americans. In addition to the known physiologic consequences of AGT, it seemed reasonable that polymorphisms in this gene might not only be associated with plasma concentrations of AGT, but also increases the risk of developing hypertension. While a number of investigators attempted to imitate the original findings of linkage and association at the AGT locus, the results have not been always concordant among the studies and have therefore aggravated intense arguments (28).

Watkins et al suggested that haplotype H4 may be a predisposing factor for EH via elevated AGT levels. In this study, activation of the RAAS system, either through sodium depletion or angiotensin II infusion, produced stronger associations between haplotype variation and hypertension-associated phenotypes. Identification of hypertensive patients with AGT haplotypes that increase plasma AGT levels could help to optimize pharmacological approaches to hypertension management (46).

The renin gene

Renin gene located on chromosome 1q32 (47) spans ~12 kb and contains eight introns (48,49). It is the first enzyme, which cleaves angiotensinogen to release angiotensin I. The precursor of rennin gene contains 406 amino acids with molecular weight 45 kDa. One segment each from the beginning (20 amino acids) and end (46 amino acids) is needed to be removed to make it active (50). Morris and Griffiths reported no connection between primary hypertension and a HindIII RFLP in the renin gene (51). Masharani and Frossard illustrated a variation by RFLP at the REN locus (52). Using the sib-pair method of linkage analysis, Naftilan et al. showed that there is no linkage by observing obligate recombinants among nine relatives with hypertension in a large Utah pedigree with a high occurrence of hypertension (53). Jeunemaitre et al. demonstrated no role for the renin gene in pathogenesis of EH (42). Frossard et al. found a statistically significant relationship between alleles on which the BglI site was present in two independent populations: one from the United Arab Emirates, a genetically homogeneous ethnic population with no history of smoking or alcohol consumption, and to a lesser degree, in a US Caucasian group that was considered for

hypercholesterolemia (54). Hasimu and co-workers discovered a new variable number of tandem repeat (VNTR) polymorphisms in intron 7 by using single strand conformation polymorphism. It was an 18bp fragment located upstream from exon 8 boundary. Nucleotide sequencing exposed that this VNTR polymorphism is a tandem repeat of the four nucleotide sequence TCTG. There were six alleles of this VNTR polymorphism, ranging from 7 to 12 repeats, but this variable region was not associated with hypertension (55,56). In a randomized double-blind clinical trial, comparing a renin antagonist, aliskiren, with an angiotensin receptor blocker, losartan, the role of 5312 renin C/T enhancer polymorphism was studied among 259 White hypertensive participants and found to be able to diminish blood pressure variation in whites suggesting the need for widespread genotyping at this locus to identify susceptibility to hypertension (57). Itani et al. recognized a single polymorphism in the enhancer region, one nucleotide downstream of the promoter distal half site of the retinoic acid response element but the variant was found to be transcriptionally silent in transfection assays carried out in renin-expressing As4.1 cells (58).

The angiotensin-converting enzyme gene

The ACE gene is positioned on chromosome 17q23 spanning 21kb and consists of 26 exons. Two promoters provide two different forms of ACE products. The widely expressed ACE gene transcribed from exons 1 to 26 except exon 13. The second promoter gives rise to a testicular form of promoters 13 to 26, which is crucial for male fertility. One more ACE homolog, ACE2, is encoded by the X chromosome and expressed in heart, kidneys, and testes and responsible for the inactivation of Ang II (59). ACE is a zinc metallopeptidase, which is extensively distributed on the surface of the endothelial and epithelial cells. Several reports suggested that there is a link in a common insertion deletion (I/D) polymorphism of a 287 bp Alu repeat in the 16th intron of the ACE gene with hypertension, atherosclerosis, renal artery stenosis, progressive kidney disease, cardiac hypertrophy, and several others. Interaction of I/D polymorphism and daily salt intake is also related to hypertension suggesting gene-environment interaction, which may be further increased by overweight (60). Recent findings suggested that the D allele is linked with diastolic hypertension (61). In the ACE gene, 78 varying sites were present that resolved into 13 distinct haplotypes (62). In humans, though the believable evidence of linkage and association of the ACE locus with serum ACE levels has been established (63), contradictory results have been published regarding association of ACE variants and hypertension (64). Studies on whites (37,65) and Japanese (19) independently reported some facts of linkage between the ACE locus and hypertension in men but not in women. However, it was also revealed that the relation between the ACE locus and hypertension was not constantly seen in men but changeable dependent on the participants' age and body weight.

Angiotensin II receptor type I

The vasoconstrictor and growth promoting effects of Ang II are mediated by the angiotensin II type 1 (AT1R) receptor. The gene for this receptor is 55kb long and contains five exons. A silent polymorphism restricted to the 3′ untranslated region of the gene with adenine changed to cytosine at position 1166 (A1166C) was reported with harsh EH (12,15,66–70). The A1166C polymorphism is connected with hypertension in Caucasians, but not in Japanese (71) and in Koreans (72). Jin et al. established that an A810T polymorphism in the promoter region of AT1 was linked with hypertension in a Chinese population. Polymorphism in the promoter region (A153G) of the AT1 gene was associated with the development of EH and coronary heart disease (CHD) (73). Eighty seven elderly subjects were studied in Chinese population for association of two SNPs of the β 2-adrenoceptor (β 2-AR) gene with hypertension in elderly patients and found that SNP at locus +1239 of β 2-AR gene was associated with hypertension in these elderly patients (74). Investigation of the angiotensin type 1 receptor (AT1R A/C 1166) on 16434 Tohoku University students was unable to locate any connection with hypertension (75).

G-proteins

G-proteins mediate the intracellular effects of various vasoactive and proliferative stimuli. Recently, G-protein signaling was found to be improved in cultured cells of a variety of hypertensive subjects. A polymorphism at position 825 (C3T) of the G-protein b3 subunit gene (GNB3) was firmly connected to this phenotype (39,44) and also drastically associated with lesser renin and prorenin levels, whereas the aldosterone-to-renin ratio was prominent in these subjects. This polymorphism does not give rise to an amino acid substitution, but the disease-type (825T) allele is associated with the occurrence of alternative splicing, which causes the loss of 41 amino acids within highly conserved repeating units of the gene. Significant links between the 825T allele and diastolic blood pressure, plasma renin, and prorenin levels (inverse), and the aldosterone-to-renin ratio persisted after adjustment for age, sex, body mass index, and systolic blood pressure. These interpretations suggest a molecular mechanism that unifies a higher diastolic blood pressure, a lower renin level, and an elevated aldosterone-to-renin ratio, i.e., a combination of characters often found in patients with arterial hypertension. Although a number of studies have attempted to imitate this relationship in a variety of populations, conflicting results have been recorded (76,77).

GNAS gene

G proteins are composed of three subunits Gα Gβ Gγ (according to their decreasing molecular weights), which are key signal transducers. Gα is a GTPase, whereas Gβ and Gγ are stable subunits of inactive G proteins. Bone calcium ion homoeostasis and mesenchyme growth abnormalities have been caused due to loss of function and gain of function mutations in the guanine nucleotide-binding protein, alpha-stimulating (GNAS) gene cause. The gene for GNAS is positioned on chromosome 20q and is highly tissue specific (78). A silent polymorphism was exposed through systematic sequencing of the gene GNB3 (C825T) (79). GN3B is the gene for the Gβ3 subunit and positioned on the short arm of chromosome 12, which has been specified as a

hypertension locus (78,79). GNAI2 –318 C>G SNP, which is one of the seven identified single nucleotide polymorphisms, impairs transcriptional activity through specific binding of Sp1 in inhibiting G subunit 2 protein, and was found to be linked with high SBP in Caucasians from Italy (80).

Other genes linked with primary hypertension

A huge family of membrane receptors that comprise 3% of all genes in our genome are G protein coupled receptors (GPCRs). Receptors for endothelins, α- and β-adrenoceptors, angiotensin II, vasopressin, and many other agonists are the typical GPCRs related to hypertension. Among these, an intron less gene on chromosome 10 coded the β-adrenoceptor gene (β1AR). Gly389Arg and Ser49Gly are the most frequent polymorphisms observed on the β1AR gene (81). Reports reveal that more than 20 various regulators of G proteins signaling (RGS2) stimulate the hydrolysis of GTP in the GTP-bound Gα subunits, thus, increasing the speediness of G protein deactivation. RGS2 is also expressed in kidneys, heart, and vascular smooth-muscle cells (82,83). The Gα subunit is important for the signaling for most vasoconstrictors, including AngII, endothelin I, noradrenalin, thromboxane, thrombin. and vasopressin, whereas it is most potentially regulated by the RGS2 (84). Augmented and prolonged vasoconstriction severs hypertension and vascular hypertrophy was reported through RGS2 knockout mice (85). In this way, RGS2 becomes a significant candidate gene for hypertension which is located on chromosome 1q31. In Japanese population, five variations in this region were observed by Yang et al. (86). All of them, however, occurred as rare mutations (<1% allele frequency). Riddle et al. also found 16 new variants in the RGS2 gene as studied on black and white American population. Among them, 2138-2139AA insertion/deletion polymorphism was found to be in complete linkage disequilibrium with 1891–1892 TC insertion deletion polymorphism. Though, in black American hypertensive population the 1891–1892 TC deletion allele was significantly increased whereas there was no effect on whites (87).

Not only RGS proteins but G protein coupled kinase (GRK) systems are also responsible for the GPCR mediated signals. Uncoupling of the activated receptors from G protein complexes takes place due to the binding of arrestins and other adopter proteins with the phosphorylated receptor. The receptor produced as the GRKs phosphorylate GPCRs. GRK4 is highly variable among the several known GRKs (88) and the 486Val variant of GRK4 is associated with salt-sensitive hypertension in Italians (89) which is also long-established in the white Australian population.

Several haplotypes that incorporated Arg65Leu and the Ala142Val variants were involved in this study (90,91). Involvement of other GRKs in pathogenesis of hypertension is also reported. An increase in the resting blood pressure and low β-adrenergic signaling is observed due to over expression of GRK2 in animal models (92). GRK2 is also associated with the regulation of endothelial NO synthase (eNOS) (93).

Similarly, GRK5 has also been connected with hypertension (94). An additional pathway for the GPCR signaling is presented by Rho and Rho kinases. RhoA along with Rac1 and Cdc42 create a subfamily within the huge family of small GTPases. A polymorphism in the rho kinase gene (ROCK2; Thr43Asn) has been recently observed. Homozygous carriers of the 431Asn allele accounted for ~5% of the observed blood pressure variations and had an increased risk for hypertension (95).

NOS3 encodes the endothelial nitric oxide synthase (eNOS) which is a potent regulator of vasomotor tone and peripheral resistance. The genotyping of biallelic variable number of tandem repeats (VNTR) in intron 4 and an exon 7 variant that lead to an amino acid change (Glu298Asp) in eNOS were done by PCR and restriction digestion. No association was recorded in a population of 114 Anglo-Celtic whites (96). The endothelial nitric oxide synthase NOS3 genotype-dependent relationship between blood pressure and physical activity was also established by using PCR (97). Endothelial and smooth muscle cells produce endothelin-1 (ET-1) which is a powerful vasoconstrictor peptide. Evidence proposed that the ET-1 gene is a candidate gene for hypertension.

Studies on two large Japanese populations exposed a significant correlation between the ET-1 K198N (G/T) polymorphism and BMI in association with hypertension ($P = 0.027$). It was also significant even after adjustment for gender and age ($P = 0.045$) and for all confounding factors ($P = 0.044$). T carriers were more susceptible to weight gain than GG homozygotes in association with hypertension (98). Case control study in Italian population showed that there is no role of Glu298Asp, T786C, and 4a/4b genetic polymorphisms within the endothelial nitric oxide synthase (e-NOS) gene in EH (99), on the other hand, a recent study reports lack of association (100).

An association between the apolipoprotein E genotype and hypertension was reported by Li et al. (101). Another single-nucleotide polymorphism (–254 C to G) in the TRPC6 gene was also related to idiopathic pulmonary arterial hypertension (102). Study of variations in thioredoxin interacting protein (TXNIP) indicates the role of this gene in EH. It exposed that in diabetic subjects, carriers of the TXNIP-T variant had 1.6-fold higher triglyceride concentrations ($P = 0.015$; $n = 136$) and 5.5 mm Hg higher diastolic blood pressure ($P = 0.02$; $n = 212$) than homozygous carriers of the common C-allele (103). EH has also been connected with -675A/T polymorphism of CYBA, a component of the NADPH oxidase system (104), methylenetetrahydro folate reductase (MTHFR) gene polymorphisms (C677T and A1298C) (105), matrix metalloproteinase (MMP-9-1562C>T) (106), three genetic polymorphisms (rs2276047, rs9886, and an insertion/deletion polymorphism in intron 1), inositol polyphosphate phosphatase-like 1 (INPPL1, SHIP2) (107), calcitonin-related peptide alpha (CALCA) gene 2bp microdeletion polymorphism (108), and plasma kallikrein gene (KLKB1) SNPs rs2304595 and rs4253325 (109). According to the known biochemical or physiological function, the chosen candidate genes are listed in Table 1 (21, 28).

Homologous chromosome regions or regions harboring particular genes that show hypertension linkage in animal models

Genes predisposing to hypertension in animal models may also be concerned in the etiology of human hypertension. To explore human disease, genes involved in animal models were considered as candidate genes (28). Studies of animal models of hypertension, particularly inbred hypertensive rats, keep

away from many of the problems that arose upon human studies. The blood pressure measurement can be done often in animals under more controlled conditions and may be more reproducible than in humans. Because of the inbred conditions and because of being raised under the same environmental conditions in animal models, the genetic homogeneity is high.

Adducin gene

Adducin is a heterodimeric cytoskeleton protein having three subunits encoded by three genes ADD1, ADD2, and ADD3 located on diverse chromosomes. Alteration in adducing function might cause hypertension through constitutive tubular sodium reabsorption as recorded in a series of experiments on hypertensive mice and human (110). Two polymorphisms S586C and G640W have been associated with hypertension (111). Comparison between the Milan hypertensive strain of inbred rats with the Milan normotensive strain showed amino acid variations of α-adducin (112). Cusi et al. reported the segregation of microsatellite markers near the α-adducin gene with association with hypertension and salt sensitivity in humans (111). Apart from this, causative genes remain to be recognized for blood pressure in rats. A "Comparative genomics strategy" was proposed by Stoll et al. (113) and 26 chromosomal regions of the human genome that should be prioritized in searches for SNPs and linkage disequilibrium testing were forecast.

Systematic genome-wide searches for linkage

During various genome screens, more than 10 chromosomal regions linked with hypertension have been detected. In these regions, numerous candidate genes are located, e.g., the genes coding for the AT II type 1 receptor on chromosome 3 (24), the β_2-adrenergic receptor on chromosome 5 (27), and lipoprotein lipase on chromosome 8 (114). The homologous region on human chromosome 17 in familial EH was observed by Julier et al. (115) by using several sibling pairs. The region of important linkage included the ACE locus, but the maximum confirmation of the linkage was reported to markers situated approximately 18 cM proximal to this locus.

Polymorphisms in a determined gene could be connected with the phenotype of hypertension in one ethnic population but not essentially in another. Therefore, diverse genes may influence the phenotype of hypertension in diverse populations (28).

Hypertension and genome-wide association studies

GWAS permit for the first time the investigation of most genetic variability due to common variants in the human genome. Application of this technology to blood pressure traits and hypertension has identified more than a dozen loci that are reproducibly associated with blood pressure traits in large cohorts. The genes closest to the variants identified are largely not suspected of involvement in blood pressure regulation; they may not be causal genes because they are chosen by proximity alone. The effect sizes of the variants identified are small and currently explain about 1% of the phenotypic variability (after correcting for major confounders such as sex, age, and BMI) (116).

Findings of GWAS are an encouraging step in blood pressure genetics, and they open the way for subsequent investigations. Further GWAS on alternative phenotypes (e.g., pulse pressure and mean arterial pressure) and on refined phenotypes (e.g., long-term average blood pressure) are expected to appear soon. One important contributor will be the International Consortium on Blood Pressure (ICBP)-GWAS, formed by joining together the CHARGE BP (117) and Global BP Gen (118) consortia, with a total sample size of close to 70 000 individuals.

Conclusion

Forgoing pre-molecular studies on the effect of various factors over BP have clearly demonstrated that there is a significant genetic influence responsible for BP variation. But, the problem, however, remained to be resolved is whether BP is influenced by a major gene effect regulated by environmental factors and/or whether multifactorial inheritance predominates. Moreover, the trait being studied so far is not a single entity but a combination of several polygenic quantitative traits which covary interactively along with the environmental covariates in different combinations in different individuals and populations. Therefore, it may be possible that the same gene variant may have an opposite effect on BP according to genetic and environmental backgrounds. The study of hypertension or BP regulation by breaking it down to several polygenic traits based on biochemical pathways may be the future course of research for pinpointing the genes for hypertension. Nevertheless, there is overwhelming evidence suggesting that the environmental factors have a major role to play as well in the development of arterial hypertension. It is generally assumed that predominance of the environmental factors' role over that of genes increases with age. However, the effects of environmental variables on BP have been found to vary from one study to another and are highly probable so that the effects of many environmental variables are only transient and not sustained. Reports are available on evidence suggesting a different mode of environmental influence on BP in Indian population in contrast to western societies. The environment and life styles of the populations differ widely in different countries and these factors may provide additional knowledge of the relative roles of genes and environment in the formation of the BP phenotype. India is inhabited by many diverse tribal and caste populations which have genetic homogeneity because of the practice of endogamy. The progress in molecular genetics has provided considerable help in understanding the genetics of hypertension. Studies of Mendelian forms of hypertension have led to the identification, or mapping, of several genes but limited to rare phenotypes of hypertension. The complex nature of the hypertension phenotype still requires large-scale studies to definitively establish the role of the specific chromosomal regions or genes discussed here, as well as to explore the effect of confounding variables, whether they are individual (sex, ethnic origin, etc.) or environmental. GWAS will help in better understanding of the genetics of blood pressure and hypertension, with potential benefits for prediction, diagnosis, and treatment. A better

understanding of gene–gene and gene environment interaction is necessary for realizing the pharmacogenetic treatment of hypertension.

Declaration of interest

The authors declare that all of them have made substantial contribution toward the writing of this article. The data presented are accurate. Accordingly, there is no conflict of interest arising whatsoever with this article.

Funding

Funding support of this work includes University Grant Commission Junior Research Fellowship contingency [JRF in Centre for Experimental Medicine and Surgery (C.E.M.S.); No.-R/Dev. (JRF-SRF)/"R"A/c /Medicine/23069] and Dr. D.S. Kothari Post-Doctoral Fellowships from the University Grants Commission [No.-F.4/2006 (BSR)/13-*581 and 604*/ 2012(BSR)].

References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–60.
2. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet 2008;371:1513–8.
3. Bahr V, Oelkers W, Diederich S. Monogenic hypertension. Med Klin 2003;98:208–17.
4. Chalmers J, MacMahon S, Mancia G, et al. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. Clin Exp Hypertens 1999; 21:1009–60.
5. Singh M, Singh AK, Pandey P, et al. Oxidative stress expedite risk of hypertension disorders: a study of total oxidant, total antioxidant & oxidative stress index on North Indian patients. Int J Appl Nat Sci 2014;3:87–98.
6. ALLHAT. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2002;288:2981–97.
7. Li H, Kong F, Xu J, et al. Hypertension subtypes and risk of cardiovascular diseases in a Mongolian population, inner Mongolia, China. Clin Exp Hypertens 2015;13:1–6.
8. Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. Lancet 2003;361:1629–41.
9. Turner ST, Boerwinkle E. Genetics of blood pressure, hypertensive complications, and antihypertensive drug responses. Pharmacogenomics 2003;4:53–65.
10. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996;272:676–80.
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;355:262–5.
12. Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. Nat Genet 1995;11:76–82.
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;79:407–14.
14. 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;10:394–9.
15. Mansfield TA, Simon DB, Farfel Z, et al. Multilocus linkage of familial hyperkalaemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p11-q21. Nat Genet 1997;16:202–5.
16. Schuster H, Wienker TE, Bahring S, et al. Severe autosomal dominant hypertension and brachydactyly in a unique Turkish kindred maps to human chromosome 12. Nat Genet 1996;13:98–100.
17. Corvol P, Persu A, Gimenez-Roqueplo AP, Jeunemaitre X. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. Hypertension 1999;33:1324–31.
18. Doris PA. Hypertension genetics, single nucleotide polymorphisms, and the common disease: common variant hypothesis. Hypertension 2002;39:323–31.
19. Higaki J, Baba S, Katsuya T, et al. Deletion allele of angiotensin-converting enzyme gene increases risk of essential hypertension in Japanese men: the Suita Study. Circulation 2000;101:2060–5.
20. Luft FC, Miller JZ, Grim CE, et al. Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. Hypertension 1991;17:1102–8.
21. Spielman RS, Ewens WJ. The TDT and other family-based tests for linkage disequilibrium and association. Am J Hum Genet 1996;59:983–9.
22. Sharma P, Fatibene J, Ferraro F, et al. A genome-wide search for susceptibility loci to human essential hypertension. Hypertension 2000;35:1291–6.
23. Rice T, Rankinen T, Province MA, et al. Genome-wide linkage analysis of systolic and diastolic blood pressure: the Quebec Family Study. Circulation 2000;102:1956–63.
24. Perola M, Kainulainen K, Pajukanta P, et al. Genome-wide scan of predisposing loci for increased diastolic blood pressure in Finnish siblings. J Hypertens 2000;18:1579–85.
25. Pankow JS, Rose KM, Oberman A, et al. Possible locus on chromosome 18q influencing postural systolic blood pressure changes. Hypertension 2000;36:471–6.
26. Levy D, DeStefano AL, Larson MG, et al. Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham heart study. Hypertension 2000;36:477–83.
27. Krushkal J, Ferrell R, Mockrin SC, et al. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. Circulation 1999;99:1407–10.
28. Kato N. Genetic analysis in human hypertension. Hypertens Res 2002;25:319–27.
29. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001;104:545–56.
30. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science 2000;289:119–23.
31. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 1995;11:241–7.
32. Nabel EG. Cardiovascular disease. N Engl J Med 2003;349:60–72.
33. Naber CK, Siffert W. Genetics of human arterial hypertension. Minerva Med 2004;95:347–56.
34. Garcia EA, Newhouse S, Caulfield MJ, Munroe PB. Genes and hypertension. Curr Pharm Des 2003;9:1679–89.
35. Luft FC. Mendelian forms of human hypertension and mechanisms of disease. Clin Med Res 2003;1:291–300.
36. Inoue I, Nakajima T, Williams CS, et al. A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription in vitro. J Clin Invest 1997;99:1786–97.
37. O'Donnell CJ, Lindpaintner K, Larson MG, et al. Evidence for association and genetic linkage of the angiotensin-converting

enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. Circulation 1998;97:1766–72.
38. Brand E, Chatelain N, Mulatero P, et al. Structural analysis and evaluation of the aldosterone synthase gene in hypertension. Hypertension 1998;32:198–204.
39. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990;86:1343–6.
40. Gaillard I, Clauser E, Corvol P. Structure of human angiotensinogen gene. DNA 1989;8:87–99.
41. Fardella C, Zamorano P, Mosso L, et al. A(-6)G variant of angiotensinogen gene and aldosterone levels in hypertensives. Hypertension 1999;34:779–81.
42. Jeunemaitre X, Soubrier F, Kotelevtsev YV, et al. Molecular basis of human hypertension: role of angiotensinogen. Cell 1992;71:169–80.
43. Caulfield M, Lavender P, Newell-Price J, et al. Angiotensinogen in human essential hypertension. Hypertension 1996;28:1123–5.
44. Caulfield M, Lavender P, Farrall M, et al. Linkage of the angiotensinogen gene to essential hypertension. N Engl J Med 1994;330:1629–33.
45. Jeunemaitre X, Inoue I, Williams C, et al. Haplotypes of angiotensinogen in essential hypertension. Am J Hum Genet 1997;60:1448–60.
46. Watkins WS, Hunt SC, Williams GH, et al. Genotype-phenotype analysis of angiotensinogen polymorphisms and essential hypertension: the importance of haplotypes. J Hypertens 2010;28:65–75.
47. Middleton-Price H, van den Berghe J, Harding A, et al. Analysis of markers on chromosome 1. Cytogenet Cell Genet 1987;46:662.
48. Qin H, Chen YH, Yip MY, et al. Reassignment of human renin gene to chromosome 1q32 in studies of a (1;4)(q42;p16) translocation. Hum Hered 1993;43:261–4.
49. Hobart PM, Fogliano M, O'Connor BA, et al. Human renin gene: structure and sequence analysis. Proc Natl Acad Sci USA 1984;81:5026–30.
50. Imai T, Miyazaki H, Hirose S, et al. Cloning and sequence analysis of cDNA for human renin precursor. Proc Natl Acad Sci USA 1983;80:7405–9.
51. Morris BJ, Griffiths LR. Frequency in hypertensives of alleles for a RFLP associated with the renin gene. Biochem Biophys Res Commun 1988;150:219–24.
52. Masharani U, Frossard PM. MboI RFLP at the human renin (ren) gene locus. Nucl Acids Res 1988;16:2357.
53. Naftilan AJ, Williams R, Burt D, et al. A lack of genetic linkage of renin gene restriction fragment length polymorphisms with human hypertension. Hypertension 1989;14:614–8.
54. Frossard PM, Lestringant GG, Malloy MJ, Kane JP. Human renin gene BglI dimorphism associated with hypertension in two independent populations. Clin Genet 1999;56:428–33.
55. Hasimu B, Nakayama T, Mizutani Y, et al. Haplotype analysis of the human renin gene and essential hypertension. Hypertension 2003;41:308–12.
56. Hasimu B, Nakayama T, Mizutani Y, et al. A novel variable number of tandem repeat polymorphism of the renin gene and essential hypertension. Hypertens Res 2003;26:473–7.
57. Moore N, Dicker P, O'Brien JK, et al. Renin gene polymorphisms and haplotypes, blood pressure, and responses to renin-angiotensin system inhibition. Hypertension 2007;50:340–7.
58. Itani HA, Liu X, Pratt JH, Sigmund CD. Functional characterization of polymorphisms in the kidney enhancer of the human renin gene. Endocrinology 2007;148:1424–30.
59. Sayed-Tabatabaei FA, Oostra BA, Isaacs A, et al. ACE polymorphisms. Circ Res 2006;98:1123–33.
60. Zhang L, Miyaki K, Araki J, et al. Interaction of angiotensin I-converting enzyme insertion-deletion polymorphism and daily salt intake influences hypertension in Japanese men. Hypertens Res 2006;29:751–8.
61. Jimenez PM, Conde C, Casanegra A, et al. Association of ACE genotype and predominantly diastolic hypertension: a preliminary study. J Renin Angiotensin Aldosterone Syst 2007;8:42–4.
62. Rieder MJ, Taylor SL, Clark AG, Nickerson DA. Sequence variation in the human angiotensin converting enzyme. Nat Genet 1999;22:59–62.
63. Tiret L, Rigat B, Visvikis S, et al. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. Am J Hum Genet 1992;51:197–205.
64. Staessen JA, Wang JG, Ginocchio G, et al. The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. J Hypertens 1997;15:1579–92.
65. Fornage M, Amos CI, Kardia S, et al. Variation in the region of the angiotensin-converting enzyme gene influences interindividual differences in blood pressure levels in young white males. Circulation 1998;97:1773–9.
66. Lapierre AV, Arce ME, Lopez JR, Ciuffo GM. Angiotensin II type 1 receptor A1166C gene polymorphism and essential hypertension in San Luis. Biocell 2006;30:447–55.
67. Kobashi G, Hata A, Ohta K, et al. A1166C variant of angiotensin II type 1 receptor gene is associated with severe hypertension in pregnancy independently of T235 variant of angiotensinogen gene. J Hum Genet 2004;49:182–186.
68. Henskens LH, Spiering W, Stoffers HE et al. Effects of ACE I/D and AT1R-A1166C polymorphisms on blood pressure in a healthy normotensive primary care population: first results of the Hippocates study. J Hypertens 2003;21:81–6.
69. Kainulainen K, Perola M, Terwilliger J, et al. Evidence for involvement of the type 1 angiotensin II receptor locus in essential hypertension. Hypertension 1999;33:844–9.
70. Bonnardeaux A, Davies E, Jeunemaitre X, et al. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. Hypertension 1994;24:63–69.
71. Sugimoto K, Katsuya T, Ohkubo T, et al. Association between angiotensin II type 1 receptor gene polymorphism and essential hypertension: the Ohasama Study. Hypertens Res 2004;27:551–6.
72. Suh I, Nam CM, Kim SJ, et al. Association analysis of the essential hypertension susceptibility genes in adolescents: Kangwha study. J Prev Med Public Health 2006;39:177–83.
73. Zhang KX, Liu TB, Xu QX, et al. Association of angiotensin II receptor type 1 gene single nucleotide polymorphism with Chinese essential hypertension complicated with coronary heart disease. Zhonghua Xin Xue Guan Bing Za Zhi 2005;33:720–3.
74. Wu H, Song X, Xiao J, et al. Two single nucleotide polymorphisms of beta 2-adrenoceptor gene in elderly patients with hypertension. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2002;19:127–9.
75. Miyama N, Hasegawa Y, Suzuki M, et al. Investigation of major genetic polymorphisms in the Renin-Angiotensin-aldosterone system in subjects with young-onset hypertension selected by a targeted-screening system at university. Clin Exp Hypertens 2007;29:61–7.
76. Kato N, Sugiyama T, Morita H, et al. G protein beta3 subunit variant and essential hypertension in Japanese. Hypertension 1998;32:935–8.
77. Beige J, Hohenbleicher H, Distler A, Sharma AM. G-Protein beta3 subunit C825T variant and ambulatory blood pressure in essential hypertension. Hypertension 1999;33:1049–51.
78. Siffert W. G-protein beta3 subunit 825T allele and hypertension. Curr Hypertens Rep 2003;5:47–53.
79. Siffert W, Rosskopf D, Siffert G, et al. Association of a human G-protein beta3 subunit variant with hypertension. Nat Genet 1998;18:45–8.
80. Menzaghi C, Paroni G, De Bonis C, et al. The -318 C>G single-nucleotide polymorphism in GNAI2 gene promoter region impairs transcriptional activity through specific binding of Sp1 transcription factor and is associated with high blood pressure in Caucasians from Italy. J Am Soc Nephrol 2006;17:S115–9.

81. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem 1999;274:12670–4.
82. Sinnarajah S, Dessauer CW, Srikumar D, et al. RGS2 regulates signal transduction in olfactory neurons by attenuating activation of adenylyl cyclase III. Nature 2001;409:1051–5.
83. Ingi T, Krumins AM, Chidiac P, et al. Dynamic regulation of RGS2 suggests a novel mechanism in G-protein signaling and neuronal plasticity. J Neurosci 1998;18:7178–88.
84. Heximer SP, Watson N, Linder ME, et al. RGS2/G0S8 is a selective inhibitor of Gqalpha function. Proc Natl Acad Sci USA 1997;94:14389–93.
85. Heximer SP, Knutsen RH, Sun X, et al. Hypertension and prolonged vasoconstrictor signaling in RGS2-deficient mice. J Clin Invest 2003;111:445–52.
86. Yang CL, Angell J, Mitchell R, Ellison DH. WNK kinases regulate thiazide-sensitive Na-Cl cotransport. J Clin Invest 2003;111:1039–45.
87. Riddle EL, Rana BK, Murthy KK, et al. Polymorphisms and haplotypes of the regulator of G protein signaling-2 gene in normotensives and hypertensives. Hypertension 2006;47:415–20.
88. Felder RA, Sanada H, Xu J, et al. G protein-coupled receptor kinase 4 gene variants in human essential hypertension. Proc Natl Acad Sci USA 2002;99:3872–7.
89. Bengra C, Mifflin TE, Khripin Y, et al. Genotyping of essential hypertension single-nucleotide polymorphisms by a homogeneous PCR method with universal energy transfer primers. Clin Chem 2002;48:2131–40.
90. Speirs HJ, Katyk K, Kumar NN, et al. Association of G-protein-coupled receptor kinase 4 haplotypes, but not HSD3B1 or PTP1B polymorphisms, with essential hypertension. J Hypertens 2004;22:931–6.
91. Speirs HJ, Morris BJ. WNK4 intron 10 polymorphism is not associated with hypertension. Hypertension 2004;43:766–8.
92. Eckhart AD, Ozaki T, Tevaearai H, et al. Vascular-targeted overexpression of G protein-coupled receptor kinase-2 in transgenic mice attenuates beta-adrenergic receptor signaling and increases resting blood pressure. Mol Pharmacol 2002;61:749–58.
93. Liu S, Premont RT, Kontos CD, et al. A crucial role for GRK2 in regulation of endothelial cell nitric oxide synthase function in portal hypertension. Nat Med 2005;11:952–8.
94. Keys JR, Zhou RH, Harris DM, et al. Vascular smooth muscle overexpression of G protein-coupled receptor kinase 5 elevates blood pressure, which segregates with sex and is dependent on Gi-mediated signaling. Circulation 2005;112:1145–53.
95. Seasholtz TM, Wessel J, Rao F, et al. Rho kinase polymorphism influences blood pressure and systemic vascular resistance in human twins: role of heredity. Hypertension 2006;47:937–47.
96. Benjafield AV, Morris BJ. Association analyses of endothelial nitric oxide synthase gene polymorphisms in essential hypertension. Am J Hypertens 2000;13:994–8.
97. Kimura T, Yokoyama T, Matsumura Y, et al. NOS3 genotype-dependent correlation between blood pressure and physical activity. Hypertension 2003;41:355–60.
98. Jin JJ, Nakura J, Wu Z, et al. Association of endothelin-1 gene variant with hypertension. Hypertension 2003;41:163–167.
99. Dell'Omo G, Penno G, Pucci L, et al. Lack of association between endothelial nitric oxide synthase gene polymorphisms, microalbuminuria and endothelial dysfunction in hypertensive men. J Hypertens 2007;25:1389–95.
100. Colomba D, Duro G, Corrao S, et al. Endothelial nitric oxide synthase gene polymorphisms and cardiovascular damage in hypertensive subjects: an Italian case-control study. Immun Age 2008;5:4.
101. Li X, Du Y, Huang X. Association of apolipoprotein E gene polymorphism with essential hypertension and its complications. Clin Exp Med 2003;2:175–9.
102. Safrina O, Yu Y. A functional single-nucleotide polymorphism (-254 C to G) in the TRPC6 gene is associated with idiopathic pulmonary arterial hypertension. Circulation 2006;114.
103. van Greevenbroek MM, Vermeulen VM, Feskens EJ, et al. Genetic variation in thioredoxin interacting protein (TXNIP) is associated with hypertriglyceridaemia and blood pressure in diabetes mellitus. Diabet Med 2007;24:498–504.
104. Moreno MU, San Jose G, Fortuno A, et al. A novel CYBA variant, the -675A/T polymorphism, is associated with essential hypertension. J Hypertens 2007;25:1620–6.
105. Markan S, Sachdeva M, Sehrawat BS, et al. MTHFR 677 CT/MTHFR 1298 CC genotypes are associated with increased risk of hypertension in Indians. Mol Cell Biochem 2007;302:125–31.
106. Zhou S, Feely J, Spiers JP, Mahmud A. Matrix metalloproteinase-9 polymorphism contributes to blood pressure and arterial stiffness in essential hypertension. J Hum Hypertens 2007;21:861–7.
107. Marcano AC, Burke B, Gungadoo J, et al. Genetic association analysis of inositol polyphosphate phosphatase-like 1 (INPPL1, SHIP2) variants with essential hypertension. J Med Genet 2007;44:603–5.
108. Morita A, Nakayama T, Soma M, Mizutani T. Association between the calcitonin-related peptide alpha (CALCA) gene and essential hypertension in Japanese subjects. Am J Hypertens 2007;20:527–32.
109. Lu X, Zhao W, Huang J, et al. Common variation in KLKB1 and essential hypertension risk: tagging-SNP haplotype analysis in a case-control study. Hum Genet 2007;121:327–35.
110. Manunta P, Citterio L, Lanzani C, Ferrandi M. Adducin polymorphisms and the treatment of hypertension. Pharmacogenomics 2007;8:465–72.
111. Cusi D, Barlassina C, Azzani T, et al. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. Lancet 1997;349:1353–7.
112. Bianchi G, Tripodi G, Casari G, et al. Two point mutations within the adducin genes are involved in blood pressure variation. Proc Natl Acad Sci USA 1994;91:3999–4003.
113. Stoll M, Kwitek-Black AE, Cowley AW, Jr., et al. New target regions for human hypertension via comparative genomics. Genome Res 2000;10:473–82.
114. Wu DA, Bu X, Warden CH, et al. Quantitative trait locus mapping of human blood pressure to a genetic region at or near the lipoprotein lipase gene locus on chromosome 8p22. J Clin Invest 1996;97:2111–8.
115. Julier C, Delepine M, Keavney B, et al. Genetic susceptibility for human familial essential hypertension in a region of homology with blood pressure linkage on rat chromosome 10. Hum Mol Genet 1997;6:2077–85.
116. Ehret GB. Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. Curr Hypertens Rep 2010;12:17–25.
117. Levy D, Ehret GB, Rice K, et al. Genome-wide association study of blood pressure and hypertension. Nat Genet 2009;41:677–87.
118. Newton-Cheh C, Johnson T, Gateva V, et al. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet 2009;41:666–76.