Int J Biol Med Res. 2011; 2(4): 1198 -1203

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Review Article

# Are Genetic factors really predisposing for essential hypertension?

**Ashwini Kamble*, Kanchan Mohod, Satish Kumar,**

**Department of Biochemistry, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India*

ARTICLE INFO

*Keywords:*
Genes
Essential hypertension
Molecular mechanism

ABSTRACT

Hypertension is a major risk factor for cardiovascular disorders such as stroke, heart failure, vascular disease, and end-stage renal disease, and is one of the leading causes of morbidity and mortality worldwide. While genes causing certain monogenic forms of human hypertension have been found; the current challenge is to identify and understand the admixture of genes causing hypertension in a majority of humans that has a polygenic basis. The convergence of global screening of gene expression patterns with extensive structural genomic information may be necessary to identify the gene clusters in hypertension that contributes to. This article reviews the recent progress, integrative efforts in the field and their extent to which genetic factors play a role in sustaining or modulating hypertension.



## 1. Introduction

Essential hypertension a major public health problem is characterised by sustained elevation of blood pressure without any identifiable cause. Both environmental and genetic factors predispose individuals to hypertension. Whereas we know much about environmental factors, such as salt intake and exercise, that affect blood pressure, less is known about the genetic factors predisposing individuals to hypertension. Genetic studies of multifactorial disorders like hypertension in human populations remain challenging because of multiplicity of genes underlying complex phenotypes, the modest nature of gene effects, and their evitable heterogeneity of the patient population. In recent years, there has been great progress in elucidating the molecular basis of monogenic disorders with primary effect on blood pressure, and this work has clarified many aspects of blood pressure regulation. Although such work has greatly expanded our understanding of molecular mechanisms underlying hypertension, pathways determining this genetic predisposition to hypertension in the general population remain unknown. For example, essential hypertension has at least 51 genes/loci that affect different physiological and biochemical systems[1] .Most of the studies done so far have utilized genetic linkage and association methods and enrolled unrelated individuals in case–control designs. The pools of studies are kept on pouring from across the globe as well as more particularly from the Asian continent. Therefore, we feel to review and recapitulate the accumulated evidence in this field to grasp how far we really reached in the genetic contribution of essential hypertension.

## 2.Candidate gene approach

Most genetic studies of hypertension-predisposing genetic loci have used candidate gene approach to study candidate genes. This systematic approach assumes that a gene or a set of genes involving a specific physiological or cellular function contribute to blood pressure variation. Utilizing this approach, some candidate genes have been elucidated from the study of rare monogenic forms of hypertension. For example genetic variations of DRD1 receptor, Na+/H+ exchanger, alpha adducine, Angiotensin II AT 1 receptor, WNK 1 and WNK 4 Kinases are found to be linked with the development of essential hypertension[2, 3 ].NKCC2 and ROMK genes are implicated in monogenic forms of essential hypertension like in Barter's Syndrome[4].In addition, Jeunemaitre et al reported that ACE was not linked to hypertension in humans[5]. Nonetheless, ACE was tested in many populations with the majority of the studies concluding that the human ACE gene was not linked to hypertension[6]. Similarly Kato N et al have clearly

* Corresponding Author : Ashwini Kamble, MD
Department of Biochemistry,
Mahatma Gandhi Institute of Medical Sciences,
Sevagram, Maharashtra, India
E.mail:dr.ashwinipravin@gmail.com

showed that there is lack of association between alpha-adducine locus and essential hypertension in the Japanese population[7 ].Because of the limited success in identifying genes involved in complex traits using linkage studies, map-based association studies and linkage disequilibrium tests have gained momentum as novel approaches, supported by the rapid development of "third generation" markers based on single-nucleotide polymorphisms (SNPs)[8, 9]. These studies require a very high density of genetic markers and sophisticated statistical tools to analyze large marker sets[10,11,12 ].Once a region is established to harbor a major disease gene, there is potential for advanced "finished" sequencing of these regions. A genome-wide association study by The Wellcome Trust Case Control Consortium (WTCCC) using 2000 cases of essential hypertension and 3000 controls represents the single largest human association study for hypertension conducted to date, wherein six SNPs were reported as being associated with hypertension. Comparative mapping revealed that the homologous locations of four out of these six human SNPs map within regions of the rat genome identified as blood pressure quantitative trait loci (QTL) containing regions originally identified from a single linkage analysis between the hypertensive Dahl Salt-sensitive (S) rat and the Lewis (LEW) rat. Further, by combining transcriptional profiling with substitution mapping of S and LEW rats, they prioritized Nr2f2 as a positional candidate locus for blood pressure control, an observation that was corroborated recently in humans through a haplotypic analysis of the WTCCC data[13]. These observations support positional identification of additional rat BP loci previously detected through the genetic analysis of S and LEW rats and encouraged studies in human populations using the candidate gene approach[4, 14 ].Because variation in a single QTL is neither necessary nor always sufficient to promote variation in a complex phenotype and because the effects of individual QTL on polygenic traits may be quite modest, it is very difficult to identify the location of QTL at the molecular level. However, by careful application of a research paradigm and by using experimental strategies in congenic and transgenic strains that greatly reduce genetic and environmental complexity, studies in Dahl rats and in SHRs have established that, in animal models of spontaneous hypertension, QTL for BP and related complex traits can be distinctly identified at the molecular level, and QTL so identified can indeed be relevant to the pathogenesis and treatment of related human disorders[15].

Levy et al selected participants from two generations of the Framingham Heart Study and found a strong evidence for a blood pressure QTL on chromosome [17,16 ].Additionally, quantitative trait linkage analysis in the Old Order Amish population found a strong association to both diastolic and to a lesser extent systolic blood pressure in the region of chromosome 2q31–34[17 ].In another recent study demonstrated a comparative genomic map for candidate hypertensive loci in humans based on the translation of QTLs between rats and humans[18 ].This study predicted 26 chromosomal regions in the human genome that are very likely to contain hypertensive genes. Genome-wide scanning (GWS) studies are a step ahead from later wherein hundreds of polymorphic markers are genotyped, identified linkage to different chromosomal regions. For example, Krushkal et al identified four regions of the genome; viz. 2q22.1–2p21, 5q33.3–5q34, 6q23.1–6q24.1, 15q25.1–15q26.1, linked to systolic hypertension [19]. Similarly few authors identified a sibling-pair linkage at a locus on chromosome 11q and chromosome 2 with SLC4A5 gene as a candidate for hypertension while other studies found no significant evidence of linkage to a single locus in the genome in populations of Chinese and Japanese origins[19, 20]. Furthermore, a meta-analysis of genome-wide linkage scans of the US Family Blood Pressure programme failed to achieve genome-wide significance[21]. This suggests that large numbers of individuals in a study might not be sufficient in the presence of ethnic and phenotypic heterogeneity.

**3.Salt-dependent/sensitive hypertension**

Williams et al described a phenotype called 'nonmodulation', which is characterized by inability to modulate aldosterone secretion and renal blood flow by angiotensin II in a subset of essential hypertensive patients[22] Recent study suggested an association of this phenotype with M235T genotype at the angiotensinogen locus[23]. One of the most commonly studied strains is the Dahl salt-sensitive(SS) rat strain, which is an inbred strain that was artificially selected from progenitor Sprague Dawley rats to obtain the maximum blood-pressure response when given a high-salt diet[24, 25]. This is considered as a "renal model" of salt sensitive hypertension as "cross-transplantation" experiments have shown that the kidney confers salt sensitivity. These authors have reflected in their conclusion that major challenge is to identify the genes within these QTLs that are associated with salt-sensitivity. Genes for which the renal transcript abundance changes during normal adaptation to a high-salt diet will include those that are important for salt adaptation, that are induced by hypertension, and that are unrelated to salt-adaptation and blood pressure control. The working hypothesis was that genes that are most likely to be important in the pathogenesis of salt sensitivity are those that do not undergo the same change in abundance in animals/strains that develop hypertension when given a high salt diet. Gene transcripts, identified by transcriptional profiling that had different abundances in the Sprague Dawley rats, a normotensive, salt-resistant strain, on two different salt diets showed that there are three elements of the RAS system; viz renin; serum and glucocorticoid kinase 1(SGK1), which activates the epithelial Na channel (eNaC); and aminopeptidase N, which metabolizes angiotensin III to IV (a blood-flow regulator). Two of these transcripts, SGK1 and aminopeptidase N, did not undergo the same change in abundance in Dahl SS rats, suggesting that they may be good candidate genes for salt-sensitive hypertension. SGK1 and aminopeptidase N genes were mapped, using radiation hybrid mapping, with respect to reported blood-pressure QTLs in the Dahl SS rat, each mapped to QTLs, determined using congenic Dahl strains, on chromosome 1[24, 26, 27]. A polymorphism of the aminopeptidase N gene that is preferentially expressed in the Dahl SS versus Sprague Dawley and Dahl salt-resistant rats has recently been identified. Physiological validation of these genes is now

being pursued with protein and activity measurements. Lee et al.[28] sought analysis of differential gene expression patterns in the kidneys of a panel of eight congenic strains, each of which carries a different low-BP QTL allele with a genetic composition that is otherwise similar to that of the hypertensive Dahl salt-sensitive (S) rat strain. Seven out of 37 differentially expressed genes were mapped to congenic regions carrying BP QTLs, but only one of these genes, L-2 hydroxy acid oxidase (Hao2), showed the congenic strain-specific pattern of differential kidney gene expression predicted by its chromosomal location. Thus, transcriptional profiling has highlighted a number of genes that encode proteins both within and outside the RAS pathway.

Another central mechanism to renal sodium reabsorption in the loop of Henle and distal-convoluted tubule, providing the route by which the transport partner of sodium and chloride exits the cell through the basolateral membrane is ClC-Kb channel. The significance of this channel to renal sodium conservation is demonstrated by the finding that patients lacking this channel have Bartter syndrome type III, characterized by salt-wasting and hypotension.4 Intriguingly, the T481S substitution examined by Jeck et al is present in 20% to 40% of the population and induces a 7-fold increase in Cl– transport by this channel in Xenopus oocytes[29] .So it is of question whether the T481S variant might increase distal renal sodium reabsorption and thereby increase blood pressure in humans. Interestingly, it is found that age-adjusted mean arterial pressure in a German study group is approximately 4 mm Hg higher in carriers of the T481S allele than in wild-type individuals (P=0.015)[30 ]Furthermore, the fact that the prevalence of hypertension (defined as blood pressure >140/90) is significantly higher in T481S carriers than in wild-type individuals (P=0.0.011). The researchers thus propose that the T481S variant leads to increased renal salt retention and consequent elevation of blood pressure. If this suggestion proves correct, it would be an important step forward in our understanding of blood pressure regulation in the general population. Physiologically, it would suggest that sodium transport in the loop of Henle and distal-convoluted tubule is rate-limited in part by basolateral chloride transport. Clinically, one might expect that hypertensive carriers of the T481S variant would derive particular benefit from thiazide or loop diuretics, which could override the effects of an overactive ClC-Kb channel.

A recent meta-analysis review showed an association between methionine-to-threonine substitution at position 235 (M235T) with an increased risk of hypertension[31]. It was suggested that this allele has a different role among different ethnic groups, with positive association for White individuals but not for Blacks or Asians[32]. However, a linkage analysis study using the affected-pedigree-member method found a linkage between AGT locus and hypertension, but no association to M235 T was found[33]. ACE gene was also implicated in the aetiology of hypertension. Most studies showed no association or linkage between ACE gene and hypertension[ 34, 35, 36 ].However, this gene-coding area carries an insertion/deletion (I/D) polymorphism within intron 16 and recently conducted studies showed that this polymorphism affects blood pressure more in male than in female subjects although the effect was found to be weak[37, 38, 39]. In one study, blood pressure values were lower in individuals carrying the homozygous CC genotype of this gene[40]. while other studies showed that the T344C allele variant of aldosterone synthase gene (CYP11B2) may be a genetic marker for low renin hypertension [41]. Only one study have reported a higher percentage of hypertensives with the T344C allele (60%) compared to normotensives[42 ].A strong association between the intron 2 conversion allele of this gene and essential hypertension was found in the White population[43]. while a haplotype analysis showed that the T-344C and A6547G, but not the T4986C, variants of this gene are associated with hypertension in females of the Anglo-Celtic population[44].

Several other studies have investigated the role of renin gene, [45] renin binding protein genes,[46] tissue kallikrein gene promoter KLK1[47] and microsatellite markers, D17S183 and D17S934[48 ].These markers were close to the ACE locus in the homology region. Two subsequent studies also found linkage to microsatellite markers on chromosome 17. However, the largest study performed to date showed no significant linkage of essential hypertension to chromosome 17.

**4.Salt-independent (resistant) hypertension**

The identification of candidate genes for salt-independent hypertension by contrasting transcriptional profiles of spontaneously hypertensive (SHR) and normotensive (WKY) rat strains, has led to the identification of 46 differentially expressed genes[49 ].Two of these i.e., monocarboxylate transporter 1 and glutathione S-transferase Y(b) subunit, significantly impact diastolic blood pressure in F2 crosses of the rats. This point to the potential value of integrating transcriptional profiling with other forms of genetic analysis e.g., backcrosses, to narrow down the number of genes identified by transcriptional profiling for further consideration. In an analogous strategy, Liang et al compared the transcriptional profiles of the renal medulla from Dahl SR rats with Dahl SS rats that were consomic for chromosome13 from Brown Norway (BN) rats, an another salt-resistant strain, on high and low salt diets[50]. Using this four-way comparison, 60 genes were identified some of them have distinct temporal patterns of expression and they include 11 beta-HSD type 1, NGF inducible anti-proliferation protein gene, 1-Cys peroxiredoxin, kynurene-3 hydroxylase, and almost all of them map to rat chromosome 13. Genomic differences on chromosome 13 and the products that result could be regulatory factors that directly influence the expression of genes on many chromosomes. These genome-wide gene interactions could also be indirect; either through downstream signalling pathways, or as a result of feedback regulation by functional alterations. In addition, the possibility of residual BN alleles on chromosomes other than chromosome 13 in SS-13BN/Mcw rats (bred at the Medical College of Wisconsin, Milwaukee) cannot be excluded.

**5.Other miscellaneous studies**

The British Genetics of Hypertension (BRIGHT) study has collected a resource of 1,634 families with at least two affected siblings (i.e., having severe hypertension) drawn from the upper

5% of the U.K. blood pressure distribution. A genomewide linkage scan was performed and identified regions of interest on chromosomes 2, 5, 6, and 9. Authors found genome wide significant evidence for linkage with hypertension and several related covariates. The strongest signals were with leaner-body-mass measures on chromosome 20q (maximum LOD p 4.24) and with parameters of renal function on chromosome 5p (maximum LODp 3.71)[51]. Pharmacogenetic studies in hypertension have begun to report larger sample sizes. Recently BP response to thiazide diuretics was evaluated in 291 unrelated Hispanic men and women using SNPs which may be of functional importance within four common cardiovascular candidate genes[52 ].After adjustment for covariates only the endothelial nitric oxide synthase GLU298ASP variant was associated with a small BP response to hydrochlorthiazide. In a separate study the prediction of BP response to irbesartan or atenolol in reduction of left ventricular hypertrophy was tested by simultaneously genotyping 74 SNPs drawn from multiple candidate genes, which might influence target response, using a minisequencing microarray approach in the 97 hypertensive participants[53]. The authors acknowledge the difficulty of appropriate adjustment of statistical analysis to account for multiple hypothesis testing and have accordingly accepted a greater stringency for statistical significance. The results indicate that plausible candidate gene SNPs from the alpha 2 adrenoceptor and b2 adrenoceptor SNPs predicted response to atenolol, whereas angiotensinogen, angiotensin-converting enzyme and aldosterone synthase SNPs were related to irbesartan response.

**6.Contribution from Indian Studies**

Numerous genetic markers have been identified in the regulation of blood pressure and essential hypertension. One such marker that has drawn substantial attention is a-adducin (ADD1) gene. Adducin, a cytoskeleton component, is a heterodimeric protein present in many tissues with a, b and γ subunits involved in cell to cell contact, cell membrane ion transport and signal transduction. It has been postulated that ADD1 may affect blood pressure by modulating renal tubular reabsorption of sodium through the activation of Na + , K + , -ATPase with the ADD1 460Trp exhibiting higher affinity for the Na + , K+, -ATPase pump. Several studies reported the relationship between ADD1 polymorphism and anti-hypertensive drug response. Ramu et al in 2010 has investigated 432 hypertensive patients and 461 healthy controls to determine the association between ADD1 Gly460Trp gene polymorphism and essential hypertension in the South Indian (Tamilian) population[54]. They however found no significant association in the genotype and allele distribution of Gly460Trp polymorphism with hypertension in their study. Further, a meta-analysis of 15 Indian studies was carried out by the same group of authors to estimate the risk of hypertension and again could not establish any relationship or risk in the development of hypertension. This is clearly in contrast to those earlier ethnic studies published from the same Caucasians, Japanese, Africans and Chinese populations whose results were not in agreement with those of the Indian studies[55, 56].

Another interesting study conducted by Randhawa et al in 2006 conducted in North Indian in Punjabi Population to determine and demonstrate association of the ACE insertion (I) or deletion (D) with essential hypertension.57 Further these authors have showed that the insertion/deletion polymorphism in the ACE gene is correlated with the circulating ACE levels. Their study is in line with the previously conducted ethnical studies in African Americans, Chinese and Japanese population wherein the significant association of the ACE D allele with hypertension has already been established[58,59].However this is in contrast with the study by Ranade et al who failed to demonstrate the association between insertion/deletion polymorphism in the ACE gene and essential hypertension [60].

**7.Conclusions**

The data so far accumulated on the pathophysiology and genetics of hypertension discussed above led us to conclude that it would be highly unlikely that a major gene will emerge from these studies. Most of the 51 genes responsible for a hypertensive phenotype have come from case-control design studies of monogenic diseases and all are kidney-specific, operating by affecting sodium balance. Although case–control design is useful in homogenous populations, these studies were performed in heterogeneous populations and thus may have higher probability of both type 1 and type 2 errors. There are no positionally cloned genes identified to date in either rodent models or the human hypertension phenotype. There can be no doubt that linkage data published thus far in both human and animal models of hypertension attest to the complex polygenic nature of the disorder but, there is still no evidence that blood pressure loci identified in rodents and humans will be the same, but it seems plausible that each linkage peak in the rodent may comprise several QTL and this may also hold true for the human condition. The reason behind the complexity of ascertaining an unequivocal link between genetics and hypertension is apparently multifactorial and therefore the field has many limitations, but as Harrap stated in his article, "Genetics might never contribute to the diagnosis of common diseases simply because of the underlying complexities of these conditions. But that does not diminish the far greater potential of genetics for prevention and treatment"[61].

**8.References**

[1] Levy D, Ehret G, Rice K, Verwoert GC, Launer LJ, Dehghan A et al. Genome wide association study of blood pressure and hypertension. Nat Genet. 2009;41: 677-687.

[2] Glorioso N Filigheddu F, Cusi D, Troffa C, Conti M, Natalizio M, et al. Alpha-adducin 460Trp allele is associated with erythrocyte Na transport rate in North Sardinian primary hypertensive. Hypertension. 39: 357–362, 2002.

[3] Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I et al. Human hypertension caused by mutations in WNK kinases. Science. 2001 293, 1107–1112.

[4] Jeck N, Konrad M, Peters M, Weber S, Bonzel K, Seyberth H: Mutations in the chloride channel gene, CLCNKB, leading to a mixed Barter-Gitelman phenotype. Ped Res. 48: 754–758, 2000.

[5] Jeunemaitre X, Lifton RP, Hunt SC, Williams RR, Lalouel JM. Absence of linkage between the angiotensin converting enzyme locus and human essential hypertension. Nat Genet .1992;1:72–75.

[6] Staessen JA, Kuznetsova T, Wang JG, Emelianov D, Vlietinck R, Fagard R. M235T angiotensinogen gene polymorphism and cardiovascular renal risk. J Hypertension. 1999; 17: 9–17.

[7] Kato N, Sugiyama T, Morita H, Kurihara H, Sato T, Yamori Y, et al. Association analysis of beta (2)-adrenergic receptor polymorphisms with hypertension in Japanese. Hypertension 2001; 37 (2): 286–292.

[8] Wang DG, Siao CJ, Berno A, Young P, Sapolsky R, Spencer J et al. Large-scale identification, mapping, and genotyping of single nucleotide polymorphisms in the human genome. Science. 1998;280:1077–1081

[9] Marshal, E. Drug firms to create public database of genetic mutations. Science .1999;284: 406–407.

[10] Lander ES. The new genomics: Global views of biology. Science. 1996;274:536–539.

[11] Collins FS, Guyer MS, and Charkravarti A. Variations on a theme: Cataloging human DNA sequence variation. Science. 1997; 278: 1580–1581.

[12] Kruglyak, L. The use of a genetic map of biallelic markers in linkage studies. Nat. Genet. 1997; 17: 21–24.

[13] Ehret GB, Morrison AC, O'Connor AA, Grove ML, Baird L, et al. Replication of the Wellcome Trust genome-wide association study of essential hypertension: the Family Blood Pressure Program. Eur J Hum Genet. 2008.

[14] Collins FS, Patrinos EA. Jordan E, Chakravarti A, Gesteland R, Walters L. New goals for the U.S. Human Genome Project: 1998-2003. Science.1998; 282: 682–689.

[15] Casari G, Barlassina C, Cusi D, Zagato L, Muirhead R, Righetti M, et al Association of the alpha-adducin locus with essential hypertension. Hypertension .1995; 25:320–326.

[16] Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, 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, 477–483.

[17] Hamet P, Pausova Z, Adarichev V, Adaricheva K, Tremblay J. Hypertension: Genes and environment. J Hypertens. 1998;16:397–341.

[18] Laloel JM, Rohrwasser A. Power and replication in case-control studies. Am J Hypertens. 15: 201–205, 2002.

[19] Krushkal J, Xiong M, Ferrell R, Sing CF, Turner ST, Boerwinkle E. Linkage and association of adrenergic and dopamine receptor genes in the distal portion of the long arm of chromosome 5 with systolic blood pressure variation. Hum. Mol. Genet. 1998; 7: 1379–1383.

[20] Sharma P. A genome-wide scan search for susceptibility loci to human hypertension. Hypertension. 2000; 35: 1291–1296.

[21] Danziger RS. Hypertension in an Anthropological and Evolutionary Paradigm Hypertension. 2001;38;19-22

[22] Williams SM. Combinations of variations in multiple genes are associated with hypertension. Hypertension. 2000; 36 (1): 2–6.

[23] Hopkins PN. Blunted renal vascular response to angiotensin II is associated with a common variant of the angiotensinogen gene and obesity. J Hypertens. 1996;14: 199–207.

[24] Rapp JP: Dahl salt susceptible and salt-resistant rats. Hypertension. 1982;4:753–763

[25] Jeunemaitre X, Lifton RP, Hunt SC, Williams RR, Lalouel JM. Absence of linkage between the angiotensin converting enzyme locus and human essential hypertension. Nat. Genet. 1992; 1:72–75.

[26] Palijan A, Dutil J, Deng AY. Quantitative trait loci with opposing blood pressure effects demonstrating epistasis on Dahl rat chromosome 3. Physiol. Genom. 2003;15:1–8.

[27]Garrett MR, Zhang X, Dukhanina OI, Deng AY, Rapp JP. Two linked blood pressure quantitative trait loci on chromosome 10 defined by dahl rat congenic strains. Hypertension. 2001; 38:779–785.

[28] Lee SJ, Liu J, Westcott AM, Vieth JA, DeRaedt SJ, Yang S, et al. Use of a panel of congenic strains to evaluate differentially expressed genes as candidate genes for blood pressure quantitative trait loci. Hypertension Res. 2003; 26: 75-87.

[29] Jeck N, Konrad M, Peters M, Weber S, Bonzel K, Seyberth H. Mutations in the chloride channel gene, CLCNKB, leading to a mixed Barter-Gitelman phenotype. Ped Res. 48: 754–758, 2000

[30] Koopmans RP, Insel PA, Michel MC. Pharmacogenetics of hypertension treatment: a structured review. Pharmacogenetics .2003;13: 705–713.

[31] Kunz R. Association between the angiotensinogen 235T-variant and essential hypertension in whites: a systemic review and methodological appraisal. Hypertension .1997; 30: 1331–1337.

[32] Stanković A, Zivkovic M, Glisić S, Alavantić D. Angiotensin II type 1 receptor gene polymorphism and essential hypertension in Serbian population. Clin Chim Acta. 2003;327(1):181-185.

[33] Caulfield M. Linkage of angiotensinogen gene to essential hypertension. NEJM .1994; 330 (23): 1629–1633.

[34] Frossard PM, Obineche EN, Elshahat YI, Lestringant GG. Deletion polymorphism in the angiotensin-converting enzyme gene is not associated with hypertension in a Gulf Arab population. Clin Genet. 1997; 51 (3): 211–213.

[35] Dzida G. Polymorphisms of angiotensin-converting enzyme and angiotensin II receptor type 1 gene in essential hypertension in a Polish population. J Med Sci Monit 2001; 7 (6): 1236–1241.

[36] Taittonen L . Angiotensin converting enzyme gene insertion/deletion polymorphism, angiotensinogen gene polymorphisms, family history of hypertension and childhood blood pressure. Am J Hypertens 1999; 12 (9): 858–866.

[37] Fornage M, Doris PA. Use of single nucleotide polymorphisms for gene discovery in hypertension. Curr Hypertens Rep. 2000; 2 (1): 23–31.

[38] Wang WY, Zee RY, Morris BJ. Association of angiotensin II type I receptor gene polymorphism with essential hypertension. Clin Genet. 1997; 15 (1): 31–34.

[39] Ono K. Lack of association between angiotensin II type 1 receptor gene polymorphism and hypertension in Japanese. Hypertens Res. 2003; 26 (2): 131–134.

[40] Castellano M. Angiotensin II type I receptor A/C 1166 polymorphism. Relationship with blood pressure and CVS structure. Hypertension. 1996; 28: 1076–1080.

[41] Tamaki S, Iwai N, Tsujita Y, Kinoshita M. Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. Hypertension.1999; 33 (1): 266–270.

[42] Davis E. Aldosterone excretion rate and blood pressure in essential hypertension are related to polymorphic differences in aldosterone synthase gene CYP11B2. Hypertension 1999; 33: 703–707.

[43] Zhu H. Contrasting associations between aldosterone synthase gene polymorphisms and essential hypertension in blacks and in whites. J Hypertens. 2003; 21 (1): 87–95.

[44] Kumar NN. Haplotype analysis of aldosterone synthase gene (CYP11B2) polymorphisms shows association with essential hypertension. J Hypertens. 2003; 21 (7): 1331–1337.

[45]Frossard PM, Malloy MJ, Lestringant GG, Kane JP. Halotypes of the human renin gene associated with essential hypertension and stroke. J Hum Hypertens .2001; 15 (1): 49–55. |

[46] Knoll A. Human renin binding protein: complete genomic sequence and association of an intronic T/C polymorphism with the prorenin level in males. Hum Mol Genet. 1997; 6 (9): 1527–1534.

[47] Yamamoto N. Identification of 33 polymorphisms in the adipocyte-derived leucine aminopeptidase gene (ALAP) and possible association with hypertension. Hum Mutat. 2002; 19 (3): 251–257. |

[48] Julier C. 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 (12): 2077–2085. |

[49] Yang CL, Angell J, Mitchell R, Ellison DH. WNK kinases regulate thiazide-sensitive Na-Cl cotransport. J Clin. Invest .2003; 111:1039–1045.

[50] Liang M, Yuan B, Rute E, Greene AS, Zou AP, Soares P, et al. Renal medullary genes in salt insensitive hypertension: a chromosomal substitution and cDNA microarray study. Physiol Genomics. 2002; 8: 139-149.

[51] Wallace C, Xue MZ, Newhouse J, Marcona AC, Onipinla AK, Burke B et al. Linkage Analysis Using Co-Phenotypes in the BRIGHT Study Reveals Novel Potential Susceptibility Loci for Hypertension. Am J Hum Genet. 2006;79:323-331

[52] Turner ST, Chapman AB, Schwartz GL, Boerwinkle E. Effects of endothelial nitric oxide synthase, alpha-adducin, and other candidate gene polymorphisms on blood pressure response to hydrochlorothiazide. Am J Hypertens .2003; 16: 834–839.

[53] Liljedahl U, Karlsson J, Melhus H, Kurland L, Lindersson M, Kahan T et al. A microarray minisequencing system for pharmacogenetic profiling of antihypertensive drug response. Pharmacogenetics .2003; 13: 7–17.

[54] Ramu P, Umamaheswaran G, Shewade DG, Swaminathan RP, Balachander J, Adithan C. Gly460Trp polymorphism of the ADD1 gene and essential hypertension in an Indian population: A meta-analysis on hypertension risk. Indian J Hum Genet .2010;16:8-15 [55]Cusi D, Barlassina C, Azzani T, Casari G, Citterio L, Devoto M, et al. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. Lancet. 1997; 349: 1353-7.

[56] Tamaki S, Iwai N, Tsujita Y, Kinoshita M. Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. Hypertension. 1999; 33 (1): 266–270.

[57] Randhawa NK, Kumar A, Matharoo K and Bhanwer AJ. Association Study of Angiotensin-Converting Enzyme Ins/DelPolymorphism with Hypertension in Punjabi Population . Indian J Hum Genet .2008;11:78-79.

[58] Nanko Y, Oshima T, Hiraga H, Matsuure H, Kajiyama G, Kambe M. Genotype of Angiotensin I Converting Enzyme Gene is a Risk Factor for Early Onset of Essential Hypertension in Japanese Population. J Lab Clin Med, 1998;131: 502-506.

[59] Wang WY. Exclusion of angiotensinogen gene in molecular basis of human hypertension: sibpair linkage and association analyses in Australian anglo-caucasians. Am J Med Genet. 1999; 87 (1): 53–60.

[60] Ranade K. Genomes scan for hypertension susceptibility loci in populations of India, Chinese and Japanese origins. Am J Hypertens. 2003; 16 (2): 158–162.

[61] Harrap S, Davidson BR, Connor J, Soubrier F, Corvol P, R Fraser R, et al. The angiotensin I-converting enzyme gene and predisposition to high blood pressure in man. Hypertension. 1993; 21: 455–460.