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ORIGINAL ARTICLE

Elevated blood pressure: Our family's fault? The genetics of essential hypertension

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Abstract

AIM: To provide an updated review on current genetic aspects possibly affecting essential hypertension (EH), and to further elucidate their role in EH.

METHODS: We searched for genetic and epigenetic factors in major studies associated with EH between Jan 2008-Oct 2013 using PubMed. We limited our search to reviews that discussed mostly human studies, and were accessible through the university online resource. We found 11 genome wide association studies (GWAS), as well as five methylation and three miRNA studies that fit our search criteria. A distinction was not made between genes with protective effects or negative effects, as this article is only meant to be a summary of genes associated with any aspect of EH.

RESULTS: We found 130 genes from the studies that met our inclusion/exclusion criteria. Of note, genes with multiple study references include: *STK39*, *CYP17A1*, *MTHFR-NPPA*, *MTHFR-NPPB*, *ATP2B1*, *CSK*, *ZNF652*, *UMOD*, *CACNB2*, *PLEKHA7*, *SH2B3*, *TBX3-TBX5*, *ULK4*, *CSK-ULK3*, *CYP1A2*, *NT5C2*, *CYP171A*, *PLCD3*, *SH2B3*, *ATXN2*, *CACNB2*, *PLEKHA7*, *SH2B3*, *TBX3-TBX5*, *ULK4*, and *HFE*. The following genes overlapped between the genetic studies and epigenetic studies: *WNK4* and *BDKRB2*. Several of the identified genes were found to have functions associated with EH. Many epigenetic factors were also correlated with EH. Of the epigenetic factors, there were no articles discussing siRNA and its effects on EH that met the search criteria, thus the topic was not included in this review. Among the miRNA targets found to be associated with EH, many of the genes involved were also identified in the GWAS studies.

CONCLUSION: Genetic hypertension risk algorithms could be developed in the future but may be of limited benefit due to the multi-factorial nature of EH. With emerging technologies, like next-generation sequencing, more direct causal relationships between genetic and epigenetic factors affecting EH will likely be discovered creating a tremendous potential for personalized medicine using pharmacogenomics.

Key words: Essential hypertension; Epigenomics; Genome-wide association study; Genes; MicroRNAs

Core tip: Essential hypertension (EH) is considered a multifactorial disease, indicating that many genetic, epigenetic, and environmental influences affect the initiation and continuance of the disease. Our goal is to provide an updated report on current genetic aspects possibly affecting EH by elucidating genetic factors' role in EH. We found 130 genes meeting our inclusion/exclusion criteria. To our knowledge, this is the first review to discuss both genetic and epigenetic factors associated with EH in one article. With emerging technologies, more direct causal relationships between

genetic and epigenetic factors with EH will likely be discovered, creating tremendous potential for personalized medicine using pharmacogenomics.

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INTRODUCTION

Approximately 1 in 3 American adults, or about 67 million people, have hypertension (HTN)[1]. According to the American Heart Association, the majority of Americans who have had first heart attacks, first strokes, or chronic heart failure had underlying HTN, a known risk factor for each condition[2]. HTN costs the United States approximately $47.5 billion annually in direct medical costs and roughly $3.5 billion annually in lost economic productivity[3].

Essential hypertension (EH), the most common form of HTN[4], is defined as an elevation in blood pressure of unknown cause and increases the risks for cerebral, cardiac, and renal complications[5]. EH is thought to be a multifactorial disease, indicating that many factors affect the initiation and continuance of the disease[6]. From a genetic perspective, many single nucleotide polymorphisms (SNPs), genes and epigenetic factors are associated with EH. This suggests that people with these hereditary factors might have a genetic predisposition to having high blood pressure. Additionally, since EH has idiopathic origins, environmental factors may also play an important role in the cause of the disease. Weight gain and dietary factors appear to have a major role in causing EH due to impaired renal function, though the mechanisms are not well understood[7].

There has been some discussion on the common disease, common variant (CDCV) and common disease, rare variant (CDRV) hypotheses and their relation to complex diseases, such as EH[8]. The CDCV hypothesis predicts that there are common disease-producing alleles/variants that are found in all human populations with a particular phenotype for a certain disease. However, insufficient data has led to scientists challenging the validity of this hypothesis and its compatibility with many diseases[9]. Meanwhile, the CDRV hypothesis predicts that diseases with genetic predispositions may not be found commonly in the diseased human population[10]. One study argued that with human lineage, diseases were more likely to favor multiple rare variations contributing to disease, rather than common variations contributing to disease[11]. This is because common variations might have external factors that would have eliminated these genes from the population, while rare variants are new, contributing to disease[12].

The purpose of this article is to provide an updated report on the current genetic aspects that could affect EH, and to further elucidate the role of genetic factors in EH. This includes summarizing genome-wide association studies (GWAS), as well as studies that identified genes with specific physiological functions. We also summarize current knowledge of the epigenetics in EH and/or HTN.

MATERIALS AND METHODS

Since genetic factors that influence EH in the literature are broad, we looked at specific categories of genetic factors and their influence on EH. Genetic marker studies were chosen since these studies looked specifically at what genes were involved with EH, and if any had specific physiologic effects. As epigenetics has become an emerging field of interest in genetics, DNA modification related to EH is also included, specifically focusing on DNA methylation and RNA regulation studies. It is important to note that a distinction was not made between genes with protective effects or negative effects, as this article is only meant to be a summary of genes associated with any aspect of EH.

For the search criteria, specific keywords used for each category of genetic and epigenetic factors are listed below in Figure 1.

Inclusion criteria

Reviews were selected if there was a primary focus on the genes and genetic factors associated with EH. Additionally, reviews between Jan 2008-Oct 2013 were chosen to obtain the most current information. Reviews were selected that discussed human studies, with little if any focus on animal studies. Reviews were also included if there was discussion of non-European populations since EH affects many ethnicities. Lastly, the results reported from the selected reviews were limited to reviews that discussed cohorts in populations greater than 1000 individuals. Cohorts with populations > 1000 people were chosen to reduce selection bias within the primary studies, and to ensure that the genes found could apply to large populations. From the articles that were selected to be in the study, the authors identified if the genes had known pathways related to EH.

For epigenetic factors associated with EH, we included articles that discussed various epigenetic modifications and their physiologic effects, as well as specific techniques such as methylation. If the studies had relevant animal data, this was included due to the fact that there is limited epigenetic information in human studies. Articles that discussed miRNA and the association with EH were also included to ensure a more thorough gathering of data. No articles for siRNA met our search criteria. Therefore, a discussion on siRNA as it relates to EH is not provided in this article.

Exclusion criteria

Reviews were excluded if the reviews involved rare types of HTN and/or were too detailed on EH physiology. While EH physiology is important, it does not contribute to the purpose of this paper in understanding the genetic

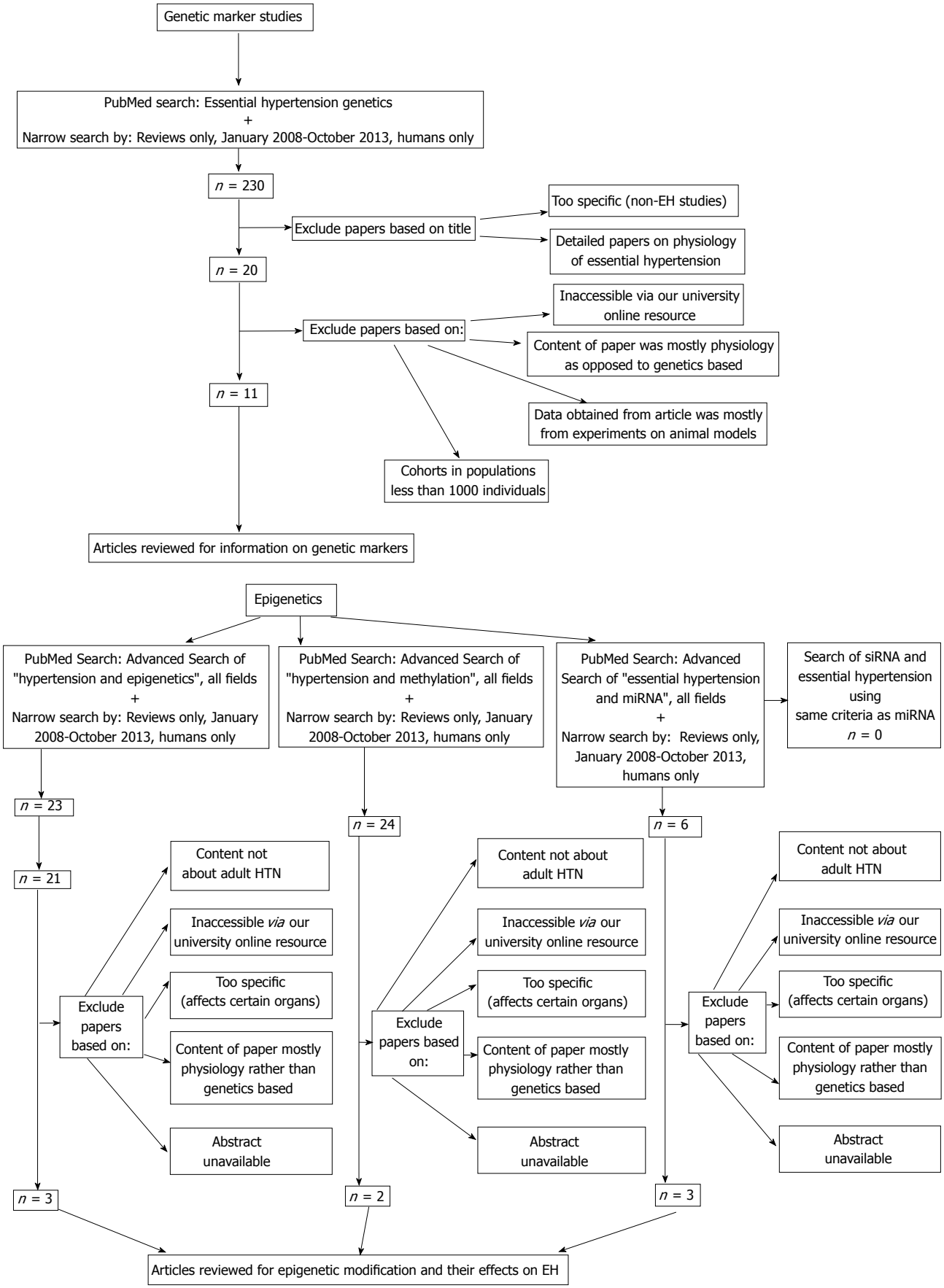

Figure 1 Search methodology for genetic and epigenetic factors associated with essential hypertension. Visual Understanding Environment v.3.2.1 (Tufts University) was used to produce the images. HTN: Hypertension.

Table 1 Genetic associations with essential hypertension according to cohort

Cohort	Genes
Framingham offspring cohort	*CCL20-WDR69, CDH13, TGFBR2,* ***STK39***
Amish cohort	***STK39***
AGEN	*NPR3,* ***CYP17A1****, FGF5,* ***MTHFR****,* ***NPPA****,* ***NPPB****,* ***ATP2B1****,* ***CSK****,* ***ZNF652***
BP-extremes	***UMOD***
BRIGHT	*BCAT1*
CARe	*c21orf91, GPR98 and ARRDC3*
CBPgen	***CYP17A1****,* ***CACNB2****,* ***PLEKHA7****,* ***SH2B3****,* ***TBX3****,* ***TBX 4****,* ***TBX5****,* ***ULK4***
CHARGE	*CPLX3,* ***PLEKHA7****,* ***TBX3****,* ***UMOD****,* ***CYP17A1****,* ***CSK-ULK3****,* ***CYP1A2****,* ***NT5C2****,* ***CYP171A****,* ***PLCD3****,* ***SH2B3-ATXN2****,* ***CACNB2****,* ***SH2B3****,* ***TBX3****,* ***TBX4****,* ***TBX5****,* ***ULK4****, c10orf107, BLK-GATA4, CASZ1, FGF5,* ***MTHFR****,* ***NPPA****,* ***NPPB****,* ***ATP2B1****,* ***CSK***
FHS	*ANKMY, FOXD3*
GBPgen	***UMOD****,* ***CSK-ULK3****,* ***CYP1A2****,* ***NT5C2****,* ***CYP171A****,* ***PLCD3****,* ***SH2B3-ATXN2****, ATXN2, c10orf107, GNAS-EDN3,* ***MECOM (MDS1 locus)****, FGF5,* ***MTHFR****,* ***NPPA****,* ***NPPB****,* ***ATP2B1****,* ***CSK****,* ***ZNF652***
GENE-centric	*SOX6, AGT, LSP1-TNNT3,* ***MTHFR****,* ***NPPA****,* ***NPPB****,* ***ATP2B1****,* ***HFE***
Health2	***ATP2B1***
HUFS	*IPO7, MYLIP, PMS1, SLC24A4, YWHAZ, CACANA1H*
Hypergenes	*NOS3*
ICBP	*ADAMTS-8, ADM, BAT2-BAT5, CHIC2-PDGFRA1, EBF1, FES, FIGN, FLJ32810-TMEM133, GOSR2, GUCY1A3-GUCY1B3, JAG1, MOV10, NOV, NPR3-c5orf23, PIK3CG, PLCE1, SLC39A8, SLC4A7, NPR3,* ***CYP17A1****, CACNB2,* ***PLEKHA7****, SH2B3, TBX3-TBX5, ULK4, GNAS-EDN3,* ***MECOM (MDS1 locus)****, FGF5,* ***MTHFR****,* ***NPPA****,* ***NPPB****,* ***ATP2B1****,* ***CSK****,* ***ZNF652****,* ***HFE***
KARE	***ATP2B1***
KORA S3	*CCNG1*
Suita study	*CCBE1*
WGHS	*BLK-GATA4, CASZ1*
Study reference not mentioned in article	*ADD1, ADD2, ADRB1, ADRB2, APOB, CACNA1A, CACNA1C, CLCNKB, CYBA, CYP11B2, CYP2C8, EDN1, EDNRA, GNB3, SCNN1A, SCNN1B, SCNN1G, SGK1, KCNJ1, ACE, ADRB2, AGT, APLNR, BDKRB2, CAPN13, CYP11B2, CYP19A, GNB3, MMP3*

Bolded genes are ones are found in multiple cohorts. The genes are identified and listed according to their respective cohorts, with a separate category to identify genes without specific references in any of the articles reviewed. Specific locations for the genes are provided where possible. Novel genes are identified, as are genes associated with physical properties.

basis for EH. Additionally, reviews were eliminated if the articles were inaccessible or the reviews focused on animal models. Genome-wide linkage studies were also exxcluded, as there was no consistency in the results for genetic markers associated with EH. Also, articles were excluded if their abstracts were unavailable. Lastly, articles were excluded if there was no access available through the library at the University of Hawaii medical school.

RESULTS

Genetic marker studies

A total of 11 genetic marker studies (genome-wide association studies) are found to contain relevant information with regards to gene associations with EH. Many of the studies identify genes within cohorts, and there are some genes identified in multiple cohorts. These can be found from references[12-21], identified in Table 1. Furthermore, some of the genes have specific phenotypic effects, or associate with other genes and/or proteins related to EH. Some of the genes found have no known function, or the authors do not list the function. These can be found in references[12-21], identified in Table 2. Genes listed with hyphens include all of the genes found inclusive of, and between, the genetic range listed.

Table 1 demonstrates the numerous amount of genes found to affect populations greater than 1000 individuals. There are several cohorts identified, each with multiple genes that are associated with EH. Also, there are some genes that are repeated in different cohorts, indicating that different populations have some genes in common with respect to EH.

Tables 1 and 2 contain the meta-analysis of two large studies with European subjects, Cohorts for Heart and Aging Research in Genetic Epidemiology Consortium and GlobalBPGen[12], which reveal fourteen loci that reached genome-wide significance. These are thought to account for 1.5% of the observed variance in blood pressure[12]. Many of the related genes have now been matched to physiologic functions (see "Known Pathway", rows 1-6) that play a role in blood pressure (BP) regulation. Further studies were done on subjects of non-European descent, including African American, Japanese, Korean, and Han Chinese populations, which are listed as "Non-European Genes". Table 2 specifically identifies the genes with known pathways related to EH regulation. Table 2 lists genes without a current known pathway to explain their influence on EH regulation.

Epigenetics and EH

Tables 3 and 4 identify many correlations between DNA and histone modifications, as well as miRNA-gene interactions and their effect on EH. Many of the genes identified were also identified through GWAS, indicating a possible mechanism for how the identified genes affect EH. It is important to note that the authors found no articles that discussed siRNA and its association with EH after conducting the literature search, thus the epigenetic section does not include siRNA.

DISCUSSION

To our knowledge, this is the first review to discuss both genetic and epigenetic factors associated with EH in one article. As one can see, many genetic factors are involved with EH. There are many genes from genetic marker studies that are found to have some association with EH, as seen in Table 2. Some genes do have known physiologic pathway associated with EH, however, many do not. Our literature review herein denotes 129 genes. Of note, genes/gene regions with multiple study references

Table 2 Genes with their identified physiological pathway and genes identified with their associated physiological functions related to essential hypertension

Genes	Pathway related to EH
NOS3	RAAS pathway[22]
SH2B3	Endothelial cell function[17]
AGT	Renal electrolyte balance[17]
NPPA	Control of extracellular fluid volume and electrolyte homeostasis[23]
NPPB	Involved in vasorelaxation and inhibition of renin and aldosterone[24]
NPR3	Involved with regulating blood volume and pressure, pulmonary hypertension, and cardiac function[25]
UMOD	Constitutive inhibitor of calcium crystallization in renal fluids[26]
CYP17A1	Involved with steroid/aldosterone synthesis. Enzyme dysfunction leads to increased levels of mineralocorticoid activating hormones[17]
ATP2B1	Codes for enzymes that have a critical role in intracellular calcium homeostasis[27]
CACNB2	Encodes for a subunit of a voltage-dependent calcium channel protein that is a member of the voltage-gated calcium channel superfamily[28]
SLC24A4	Encodes for a member of the potassium-dependent sodium/calcium exchanger protein family[29]
YWHAZ	Protein interacts with insulin receptor substrate 1 protein, suggesting a role in regulating insulin sensitivity[30]
ADAMTS-8	Enzyme encoded by the gene disrupts angiogenesis *in vivo*[31]
ADM	Protein encoded by gene may function as a hormone in circulation control[32]
c5 site between *SUB1* and *NPR3*	SNP associated with SBP NPR3 encodes natriuretic peptide receptor C/guanylate cyclase C for natriuretic peptide clearance[33-35] Also found relationship with DBP
CACANA1H	Codes for α1 subunit of voltage-dependent calcium channel for heart contractions and associated with SBP in African Americans[36]
ENPEP	Facilitates production of angiotensin Ⅱ in RAAS pathway and associated with SBP and DBP[33]
ADD1 and *ACE*	ADD1 codes for α-adducin protein that interacts with sodium channel of Na/K co-transporter and Na/K ATPase[37] Angiotensin converting enzyme produces angiotensin-converting enzyme which converts angiotensin Ⅰ to angiotensin Ⅱ in RAAS pathway[38]
ADD2	β-adducin is a cytoskeletal actin-binding protein implicated in glomerular lesions[39]
CYP11B2	Contributes to aldosterone synthesis in RAAS pathway[40]
AGT	Encodes angiotensinogen in RAAS pathway[41]
LOC344371 and *RASGRP3*	Activation decreases vascular responsiveness to endothelin-1 and angiotensin Ⅱ in rats[41]
EDN3	Endothelin-3 involved in vasoconstriction[42]
BCAT1	Associated with salt sensitivity[43]
CASZ1	Zinc-finger transcription factor that is associated with DBP[33]
ADRB2	Ion channel involved with regulation of vasoconstriction[12]
CYP11B2	Enzymatic defects results in decreased aldosterone and increased salt-wasting[12,17]
MMP3	Gene variants affect arterial stiffness and endothelial function[44]
NR3C2	Involved with aldosterone signaling[12]
SCNN1B	C terminus deletion leads to reduced ENaC clearance and increased ENaC activity[12]
APLNR	Mediator of cardiovascular disease[45]
BDKRB2	Involved in catecholamine synthesis[46]
MTHFS	Involved with catecholamine binding[47]
SOX6	Required in transcription for maintenance of cardiac and skeletal muscle cells[17]
CACNA1A	Involved with regulating SBP[48]
CCNG1	Involved with regulation of SBP and DBP and is component of regulating hypertension[15]
CPLX3	Involved with regulating DBP[15]
CSK	Cytoplasmic tyrosine kinase involved with angiotensin Ⅱ-dependent vascular smooth muscle cell contraction[17]
CACNA1C	Regulates calcium influx after depolarization[49]
CLCNKB	Involved in renal salt absorption[50]
EDN1	Endothelin-1 involved in vasoconstriction[51]
EDNRA	Endothelin receptor type A involved in vasoconstriction[52]
KCNJ1	Potassium channel involved with potassium homeostasis[53]
SCNN1A	Involved with renal sodium regulation[54]
SCNN1B	Involved with renal sodium regulation[55]
SCNN1G	Involved with renal sodium regulation[56]
SGK1	Activation of certain potassium, sodium and chloride channels, playing a role in cellular stress response[57]
SLC12A1	Cotransporter involved in sodium and chloride reabsorption in the distal convoluted tubule[58]
SLC12A3	Cotransporter involved in sodium and chloride reabsorption in the loop of Henle[59]
TNNT3	Involved in calcium-induced muscle contraction[60]
WNK1	Kinase involved with sodium and chloride transport[61]
WNK4	Kinase regulates balance between sodium chloride and potassium reabsorption in kidneys[62]
GOSR2	Interacts with target-localized SNAREs, allowing angiotensinogen to move between Golgi compartments, possibly leading to vasoconstriction[63]
GUCY1B3	Receptor for nitric oxide involved with vasodilation[64]
ATXN2	Possible association with regulation of GFR[65]
SLC4A7	Possible transporter of sodium and bicarbonate ions[66]
CDH13	Regulates endothelial cell growth[67]
Identifier information	Gene
Non-European genes	*NPR3*, *IPO7*, *MYLIP*, *PMS1*, *SLC24A4*, *TBX3*, *YWHAZ*, *FIGN-GRB14*, *ALDH2*, c5 site between *SUB1* and *NPR3*, *CACANA1H*, *SNP* upstream of *CCBE1*, *ENPEP*, *ST7L-CAPZA1*
Gene-gene interaction	*ADD1* and *ACE*, *ADD1* and *ADD2*, *ADD1* and *CYP11B2*, *AGT* and *ACE*, *c20q12*, *IMPG1*, *LOC344371* and *RASGRP3*, *PCDH15*, *NPR3-c5orf23*, *CSK-ULK3*, *BAT2-BAT5*, *BLK-GATA4*, *GNAS-EDN3*
Gene-environment interaction	Body Mass Index: *ADD1*, *ADRB2*, *CAPN13*, *CYP11B2*, *CYP19A1*, *MMP3* Black, Male: *AGT* Level of physical activity: *GNB3*, *NR3C2*, *SCNN1B*, *APLNR*, *BDKRB2* Oral contraceptive use: *COL25A1* Preterm birth: *MTHFS*
Unknown function/ function could not be determined	*GNAS-EDN3*, *NPR3-c5orf23*, *BLK-GATA4*, *ST7L-CAPZA1*, *CSK-ULK3*, *FIGN-GRB14*, *c10orf107*, *c21orf91*, *LSP1-TNNT3*, *GNAS-EDN3*, *BAT2*, *IPO7*, *MYLIP*, *PMS1*, *TBX3*, *TBX4*, *TBX5*, *ANKMY*, *BAT2*, *BAT3*, *BAT4*, *BAT5*, *ALDH2*, SNP upstream of *CCBE1*, *BCAT1*, *PCDH15*, *c20q12*, *IMPG1*, *CAPN13*, *CYP19A1*, *GNB3*, *COL25A1*, *PCDH15*, *IMPG1*, c5 site between *SUB1* and *NPR3*, *CHIC2-PDGRA1*, *APOB*, *HFE*, *CYPBA*, *CYP1A2*, *CYP2C8*, *EBF1*, *FES*, *FGF5*, *FIGN*, *FLJ32810*, *GNB3*, *LSP1*, *NOS3*, *TMEM133*, *FOXD3*, *GPR98*, *ARRDC3*, *GUCY1A3*, *JAG1*, *MECOM* (MD1 locus), *MOV10*, *NOV*, *NPR3-c5orf23*, *NT5C2-CYP171A*, *PIK3CG*, *PLCD3*, *PLCE1*, *PLEKHA7*, *RPL6-PTPN11-ALDH2*, *SLC39A8*, *ULK4*, *ZNF652*, *CCL20*, *WDR69*, *TGFBR2*, *STK39*

Only genes with pathways related to EH were identified. Genes identified with their associated physiological functions associated with EH. If there were genes that coded for proteins, but these proteins were not found to affect EH, then it was listed as unknown function or the function could not be determined. Genes with hyphens indicate genome wide association studies associated genomic regionsin, in which the genetic pathway could not be determined and properly evaluated for its involvement with EH. EH: Essential hypertension; RAAS: Renin-angiotensin-aldosterone system; SBP: Stolic blood pressure; DBP: Diastolic blood pressure.

Table 3 DNA methylation and histone modification associated with essential hypertension

Ref.	Study	Subjects	Results	Site of modification and type
Smolarek *et al*[68]		Humans	5-mC significantly higher in healthy subjects than entire group of patients with EH	N/A
Wang *et al*[69]		Humans	Increased methylation levels observed at 2-CpG sites in comparison with normotensive controls	*SULF1*: Methylation
Liang *et al*[70]		Humans	Regulation of renal sodium reabsorption β-2 adrenergic stimulation → inhibition of histone deacetylase-8 in kidney → increased histone acetylation and decreased genetic transcription of WNK4 caused increased blood pressure 11β-hydroxysteroid dehydrogenase type 2–converts active glucocorticoids to inactive glucocorticoids Promoter methylation of *HSD11B2* gene decreased expression of renal 11β-hydroxysteroid dehydrogenase type 2 affects regulation of volume and BP homeostasis ENaCα-epithelial sodium channel–affects Na+ reabsorption in the distal nephron Proposed mechanism: Methylation of Lys79 of histone H3 suppresses ENaCα transcription ACE1-Angiotensin-converting enzyme ACE1-up-regulated in association with increased binding of histone 3 acetylation (H3Ac) and 4th lysine trimethylation (H3K4me3) and in association with decreased binding of histone ninth lysine residue demethylation (H3K9me2)	*WNK4*: Decreased transcription and increased histone acetylation *HSD11B2*: Promoter methylation ENaCα: Methylation of Lys79 of histone H3 *H3K4me3*: Histone 3 acetylation and 4th lysine trimethylation. *H3K9me2*: Decreased binding of histone 9th lysine residue demethylation
Udali *et al*[71]	Friso *et al*[72]	Humans	11β-hydroxysteroid dehydrogenase 2 methylation at HSD11B2 promoter in DNA of PBMCs of hypertensive patients inversely related to enzyme function Promoter methylation of HSD11B2 gene plays a role in HTN	*HSD11B2*: Methylation in promoter region
	Lee *et al*[73]	Rats	Na^+-K^+-2 Cl^- cotransporter 1 (NKCC1) Methylation status of NKCC1 promoter–elevated in hearts of spontaneously hypertensive rats SHRs–significant hypomethylation of NKCC1 associated with increase in gene expression contributing to HTN	*NKCC1*: Methylation in promoter region *NKCC1*: Hypomethylation in promoter region
	Riviere *et al*[74]	Human endothelial cell lines and rats *in vivo*	Somatic angiotensin-converting enzyme (= ACE1) Promoter methylation levels: Higher levels of methylation associated with transcriptional repression Therefore hypomethylation of promoter region of sACE could contribute to HTN	*sACE*: Methylation in promoter region
Millis[75]		Human	Methyl CpG binding protein-2 (MECP-2) Methylates and thereby silences the expression of the norepinephrine transporter gene Phenyl-ethanolamine N-methyltransferase (PMNT)–converts Norepinephrine into Epinephrine Also mimics gene-silencing actions of MECP-2 Leads to increased synaptic levels of catecholamines (increased Epinephrine release and decreased Norepinephrine reuptake) CTGF Lysine methyltransferase that methylates the histone H3K79 site of nucleosomes that inhibits the expression of CTGF (in the cells of the collecting ducts)	*MECP-2*: Methylation *PMNT*: Methylation *H3K79*: Methylation of histone site of nucleosomes

As demonstrated in Table 3, many of the genes identified undergo methylation. If the reviews discuss results from individual studies, then the separate studies are placed in the second column. The results are listed based on the gene/site of modification, along with a description of what occurs as a result of the modification. The last column provides a summary of the gene/site of modification and the type of modification that occurs at that particular site. CTGF: Connective tissue growth factor.

include: *STK39*, *CYP17A1*, *MTHFR-NPPA*, *MTHFR-NPPB*, *ATP2B1*, *CSK*, *ZNF652*, *UMOD*, *CACNB2*, *PLEKHA7*, *SH2B3*, *TBX3-TBX5*, *ULK4*, *CSK-ULK3*, *CYP1A2*, *NT5C2-CYP171A*, *PLCD3*, *SH2B3-ATXN2*, *CACNB2*, *PLEKHA7*, *SH2B3*, *TBX3-TBX5*, *ULK4* and *HFE*. The following genes overlap between the genetic studies and epigenetic studies: *WNK4* and *BDKRB2*. While *WNK4* and *BDKRB2* are found in both genetic and epigenetic studies, it appears that *WNK4* (kinase regulates balance between sodium chloride and potassium reabsorption in kidneys), and *BDKRB2* (involved in catecholamine synthesis) may be associated with EH through interactions with miRNA.

Prior to GWAS, studies were somewhat successful in isolating genes associated with rare monogenic forms of hypertension that are inherited in a classic Mendelian fashion. The introduction of GWAS has made it possible to identify novel loci that could not be predicted physi-

Table 4 MiRNA targets associated with essential hypertension

Ref.	Subjects	Results	miRNA targets
Xu *et al*[76]	Human plasma	hcmv-miR-UL112; miR-605; miR-623; let-7e;miR-516b; miR-600; kshv-miR-K12-6-3p; miR-602; miR-1252 miR-296-5p; miR-133b; miR-30 d; miR-625*; miR-1236; miR-518b; miR-1227; miR-664; miR-615-5p; miR-18b*; miR-1249; miR-324-3p; ebv-miRBART17-3p; miR-634; ebvmiR-miRBART19-5p; miR-486-5p; kshvmiR-K12-10a; kshv-miR-K12-10b	INF-1 is direct target of hmcv-miR-UL112 Indicates link between CMV infection and EH
Batkai *et al*[77]	Human	Endothelial miRNA	
		miR-126	SPRED-1; PIK3 regulatory subunit-2; VCAM-1; CXCL12;
		miR-217	
		miR-122	RhoB
		miR-21	SirT1
		miR-24	SLC7A1
		miR-27b, -130a, -210, -378, -17–92, let-7f	Nitric oxide pathway Hypoxia-induced mechanism
		miR-15, -16, -20a, -20b, -24, -221, -222	Pro-angiogenic Anti-angiogenic
		Renal miRNA	
		miR-29b	Fibrotic pathway; collagen genes; *Mmp2*; *Itgb1*
		miR-200a, miR-200b,	
		miR-141, miR-429, miR-205, miR-192	Biomarkers of nephrosclerosis
		miRNA targeting RAAS	
		miR-155	*AGTR1*
		miR-526b and -578	*AVPR1A*
		miR-34a, and -34c	*BDKRB2*
		miR-765	*TBXA2R*
		miR-383	*NR3C2*
		miR-9	*NFATc3*
		miR-124 and miR-135a	*NR3C2*
		miRNA targeting smooth muscle cells	
		miR-143 and miR-145	Actin stress fibers;
		miR-21	ACE; KLF5;
		miR-21, -26b, -98, and -1826	myocardin; MRTF-B; calmodulin kinase II-δ
		miR-221 and -222	PTEN; Bcl-2; cGMP signaling
		miRNA in other etiologic factors	Nitric oxide and ANP pathway
			p27(Kip1), p57(Kip2) and/or c-kit
		miR-296-5p, let-7e, hcmv-miR-UL112	Association with hypertension
		hcmv-miR-UL1	IRF-1
		miR-637	*ATP6V0A1*, chromaffin granule function
Fung *et al*[78]	Human	miR-155	Suppress expression of *AGTR1*

Table 4 demonstrates how miRNAs affect different aspects of blood pressure regulation. Also, there appears to be a link between cytomegalovirus (CMV) infections and essential hypertension; miRNA has been identified as a possible mediator of this connection. The asterisk identified for some miRNAs[78] are not defined in the original article, but are assumed to be a part of the proper notation for that miRNA. EH: Essential hypertension.

ologically, using non-family cohorts.

This review shows that no Mendelian variants or epigenetic factors are consistently associated with EH in the large cohort studies examined. Furthermore, it was not possible for the authors to correlate the epigenetic factors associated with the pathways identified, as there were no clear relationships between EH and the individual genes. Therefore, it can be inferred that EH follows multifactorial inheritance and insinuates that it follows the CDRV genetic hypothesis. In regards to identifying rare variants, GWAS is used for polymorphism detection, and is not set up to identify SNPs with low mean allele frequencies (MAFs) (low MAFs are usually under 1%, and sometimes even as high as 5%). Therefore, other techniques will need to be used to identify rare variants. Next-generation sequencing has revolutionized our ability to sequence thousands of genes at one time in a cost-effective manner. Using full exome or full genome sequencing of EH cohorts, next-generation sequencing will help to identify rare, as well as low-MAF, variants associated with regulating blood pressure[12]. This will likely show the exact genetic factors responsible for EH instead of mere associations which have been the mainstay of our genetic search using GWAS. Similar high throughput techniques will likely also improve our identification of epigenetic regulators.

Insufficient evidence was found in this study to pursue single site genetic marker or epigenetic testing to provide a simple genetic risk assessment for EH. Genetic algorithms comprised of information from multiple genes and epigenetic factors, along with family history and environmental variables, could potentially be developed to provide a genetic risk assessment for EH. However, it will be difficult to know what to do with this data, since preventative factors such as exercise and a healthy diet would be recommended to anyone at any level of personal and/or family history risk for EH. A similar concept was examined in a recent publication evaluating genetic testing and type 2 diabetes[79]. The evaluation of genomic applications in practice and prevention (EGAPP) consortium recommend against using genetic diabetic markers for risk assessments since it would be of limited benefit[79]. Additionally, for cardiovascular morbidity, current non-genetic algorithms already exist[80,81] that assess the risk of heart disease using a patient's medical profile.

Although risk assessments may be difficult, pharmacogenomic utility may be found by studying risk alleles in individuals and treating their HTN in a personalized manner based on the pathway affected to obtain optimal blood pressure control[13].

To our knowledge, this is the first review to discuss both genetic and epigenetic factors associated with EH in one article. Insufficient evidence was found in this review to pursue any one single genetic test to provide a genetic risk assessment for EH.

In conclusion, while there exist genetic and epigenetic associations that play a role in EH, there are still no well-established cause-and-effect relationships for the development of EH. With emerging technologies, such as next-generation sequencing, a more direct relationship may be established between genetic and epigenetic factors and EH. Extensive algorithms for EH will likely need to be developed to incorporate these genetic risk factors, in concert with a patient's personal risk factors. However, the utility of this approach will need to be proven. There is a large potential for personalized medicine through pharmacogenomics that will come from our better understanding of the genetic factors and pathways involved in EH.

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COMMENTS

Background

Essential hypertension (EH) is thought to be a multifactorial disease, meaning that environmental and genetic factors affect the initiation and continuation of the disease. While there have been several publications discussing the genetic factors involved with EH, to date there has been no single publication that has discussed both genetic and epigenetic factors in one article.

Research frontiers

While EH is thought to be a multifactorial disease, several genetic factors have been associated with EH. In the area of genetic and epigenetic factors associated with EH, their remains a need to review the most updated information regarding genetic and epigenetic factors and discuss both in one article.

Innovations and breakthroughs

Previously, scientists would have to refer to Genome-wide association studies and epigenetic studies to understand how genetic and epigenetic factors are associated with EH. This is the first review article to discuss both genetic and epigenetic factors in one article. Also, this article discusses the most current up-to-date literature, providing a more recent understanding of genetic factors associated with EH.

Applications

Next-generation sequencing will allow scientists to analyze thousands of genes in a cost-effective manner. Using full exome or full genome sequencing of EH cohorts, next-generation sequencing will help to identify rare, as well as, low-mean allele frequency variants associated with regulating blood pressure. This will be useful in the growing field of pharmacogenomics, where medical regimens are being tailored to individuals based on specific genetic polymorphisms. This will help to personalize treatment regimens and improve the care given to patients with EH.

Terminology

Essential hypertension is a form of hypertension that has no known cause, but is responsible for most cases of hypertension. Genome-wide association studies look at the whole genome of populations of individuals who suffer from a specific condition to see if these individuals have any genes that differ from the general population without the condition in question. Pharmacogenomics is an emerging field where scientists and doctors use someone's genetic code to determine appropriate doses for medications to ensure fewer side effects and the best possible therapy.

Peer review

The present study appears well conducted for design and contents. Inclusion criteria and exclusion criteria are reasonable.

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