Review Article

Epigenetic alterations in hypertension

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ABSTRACT

Abstract

Hypertension is a chronic condition that develops due to genetic and environmental factors. Primary hypertension exists independently of all other diseases, which develop as a result of genetic influence and modification by environmental conditions. Genetics, epigenetics, age, obesity, smoking, diabetes, and arterial aging represent the most critical risk factors for primary hypertension. In addition, genetic variants contributes importantly to hypertension development. Genetic expressions are influenced by several factors, including but not limited to chemicals, aging, dietary factors, and drugs, through different epigenetic processes that may yield different epigenetic patterns even among monozygotic twins. Several studies have established that alterations in these epigenetic processes are implicated in the pathogenesis of various diseases, including hypertension. The current review provides an overview of the genetic and epigenetic changes associated with hypertension (HTN). Since DNA methylation-based biological age metrics may lead to improvements in early intervention approaches to hypertension, their use in further research could not only enhance but also significantly contribute to the development of personalised prevention strategies and treatment methods.

Keywords

Hypertension; DNA methylation; Epigenetics

INTRODUCTION

Hypertension (HTN) is a common chronic condition among older adults. However, it is expected to affect many adults worldwide[1] . HTN is a significant risk factor for kidney disease and various cardiovascular problems, including stroke, coronary artery disease, peripheral vascular disease, and heart failure[2,3]

Multiple factors, including genetic, metabolic, and environmental influences, significantly contribute to the development of hypertension[4] . Advanced age, gender, physical activity, obesity, diabetes, elevated sodium levels, and excessive alcohol consumption are all risk factors for the occurrence of hypertension[5,6] .

Depending on the origin, hypertension (HTN) can be classified into two groups: primary, essential hypertension, and secondary, as well as non-essential hypertension. Primary hypertension occurs in approximately 95% of individuals, while secondary hypertension affects about 5%. The aetiology of primary hypertension involves genetic and environmental factors. Notable contributing factors include genetic predisposition, epigenetic alterations, age, obesity, smoking, diabetes, and the aging of arterial systems, all of which are significant in the development of hypertension[7,8]. Conversely, secondary hypertension resulting from endocrine disorders and renal diseases also contributes to disease onset[9].

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Genetic Factors in Hypertension

Genetic alterations are crucial in the development of hypertension. Single gene mutations linked to Liddle syndrome, aldosterone-producing adenomas, and pseudohypoaldosteronism have been identified as factors in heritable forms of hypertension following Mendelian inheritance patterns[10]. Several genes play a pivotal role in HTN development; familial history is an essential factor in HTN [11]. Studies on family members and twins have revealed that the genetic transmission rate ranges from 30% to 60%[12].

Mineralocorticoid, glucocorticoid or sympathetic pathway mutations are important in genetic forms of HTN[13]. CYP11B1, CYP11B2, SCNN1G, WNK1 and WNK4 gene variations have been related to HTN development [14]. Corin is responsible for synthesising active natriuretic peptides that inhibit the development of hypertension[5]. Genome-wide association studies (GWAS) have identified over 1000 SNPs [15].

Research has demonstrated that the Klotho (KL) gene has a crucial function in essential hypertension (EH) [16,17] , and over 10 SNPs related to EH have been identified in the KL gene[16,17]. Earlier studies have shown that KL deficiency may lead to the development of HTN. [18] Hypertension associated with KL deficiency is aligned with increasing oxidative stress, still, the oxidative stress levels that conserve KL genes can be reduced with a pharmacologically sufficient pro drug, ATR108 and ATR158[18] . Association studies suggested that KL gene polymorphisms were positively associated with vascular endothelial function and low blood pressure by stimulating the NO-mediated signaling pathways[19] . In hypertensive patients, serum IGF-1 level was elevated, but KL may target insulin or IGF-1 signaling pathway to minimize oxidative stress in animals [20].

The circadian clock is a stable trait for organisms that helps them respond to external cues within a 24-hour time frame. The clock is involved in various physiological processes, including sleep-wake cycles, immune system function, metabolic activities, kidney function, and blood pressure regulation. Moreover, it is also required for the maintenance of vascular homeostasis. Research reveals that disrupted circadian clock function contributes to adverse conditions, such as vascular disease and hypertension, through mechanisms of vascular dysfunction[21]. It is known that the circadian clock regulates blood pressure and circadian rhythm. It ensures that blood pressure in people with normal bodily functions decreases at night and increases the following day in the morning, which further helps protect human health[7]. Manipulating renal, cardiac and vascular physiology to control hypertension has been hypothesized by several researchers. Specifically, dysregulation of circadian clocks has been identified as one such factor, potentially leading to a disrupted coupling of the physiological internal clock with environmental cues, including light, that has been linked to the onset of several diseases, including hypertension (HTN)[22]. It is noteworthy that the most susceptible to such a circadian disturbance due to any number of reasons, such as shiftwork or chronic jet lag, develop a myriad of subsequent adverse health consequences, such as, but not limited to, hypertension (HTN). Additionally, several epidemiological studies have reported an association of circadian clock genes with hypertension [19,23].

Epigenetic alterations in hypertension

Epigenetics can be best described as an inheritable and non-DNA sequence-dependent modification of the expression of a particular trait. Through this process, the 'information' concerning the expression of a specific set of genes can be reliably passed on to daughter cells, and it also helps to explain the different patterns of gene expression found in different cell types. Some modifications classified as epigenetic changes include post-translational addition of chemical groups to histones, modification of the DNA structure such as methylation, remodelling of active DNA and modification of ribonucleic acid. Such modifications are crucial in regulating the activity of genes and the biological response of cells to various signals[24] .

DNA methylation is a biological process that alters gene expression by attaching methyl groups to the carbon 5 of cytosine bases present within the CpG dinucleotides. This change might result in the silencing of gene expression, but this is reversible[23,24,25]. Furthermore, DNA methylation plays a role in regulating genes that influence blood pressure (BP) levels in humans. Abnormal methylation of genes involved in renal sodium retention, the renin-angiotensin and aldosterone system, and the sympathetic nervous system has been linked to the development of hypertension [26]. Understanding these mechanisms may aid in the development of strategies for future patient treatment.

According to Kato et al.[22], there are certain links

between the ion channels controlled by blood pressure (BP)—12 in total—and SNPs. Alterations in DNA hypermethylation of the genes related to the RAS and SNS are a crucial factor in the development of HTN. With the help of Angiotensin II (Ang II), which binds to the angiotensin type 1 and 2 receptors (AT1a, AT1b and AT2R), blood pressure is controlled[22]. Moreover, Han et al. [23]note that abnormal functioning of AT1R has been proven to exacerbate the effect of Ang II on renal blood vessels, resulting in the worsening of hypertension[23].

Research showed that in spontaneously hypertensive rats, the expression of the gene AT1a was expressed more than in their age mates, Wistar-Kyoto rats. It was suggested that hypomethylation of the AT1a promoter region was responsible for the elevated AT1a expression observed in SHRs [26]. Studies have shown that nicotine use in pregnant rats leads to their offspring being hypertensive due to AT1a expression upregulation due to hypomethylation[27,28]. Pregnant rats on low-protein diets were also reported to give birth to hypertensive offspring, and this has been related to hypomethylation of the AT1b promoter and the overexpression of this gene[29]. On the other hand, it has been suggested that high maternal glucocorticoids in early pregnancy might reduce methylation of the AT1b promoter, which enhances the expression of AT1b. Therefore, it is worthwhile to note, these studies suggest there is a potential causal link between the aberrant methylation of the angiotensin II type 1 receptor (AT1R) gene and the development of hypertension [30].

The ACE enzyme biochemically transforms the inactive construct known as angiotensin I (Ang I) into a more stable and active form, angiotensin II (Ang II). This formation of Ang II, in turn, causes an increase in the blood pressure (BP) levels within the body. It has been established that having a maternal low-protein diet (MLPD) during fetal brain formation causes a child's ACE-1 gene's expression to be affected in the brain due to the hypomethylation environment around the ACE-1 [31]. Also explored is the connection between ACE gene methylation and hypertension, with low-birth-weight children correlating negative ACE methylation levels with BP [32]. Endothelin converting enzyme-1 (ECE-1), having the strongest correlation in increasing inflammation through endothelin-1, has a potent vasoconstrictor function, which is the main point of realisation in the research. The ECE-1 gene located within endothelial cells, through methylation, decreases the ECE-1 promoter level, which in turn shows that the methylation process dips associating the ECE-1 expression that relates to hypertension [23,33]. Adducin (ADD), which is a heteromeric protein column, is made up of αβ or αγ subunits, the α-subunit being encoded by the ADD1 gene[34].

A strong association has been encountered between the ADD gene and essential hypertension [35]. Furthermore, low methylation levels of the ADD1 promoter have been proven to increase the chances of patients acquiring hypertension[36]. The enzyme 11 beta-hydroxysteroid dehydrogenase 2 (11bHSD2) can convert cortisone to cortisol, and this same enzyme plays a crucial role in sodium reabsorption in the kidneys. Lower levels of 11bHSD2 can be causal factors for developing higher blood pressure and inducing hypertension[23].

In recent findings, it could be stated that there has been substantial hypermethylation of the 11BHSD2 promoter region in people suffering from essential hypertension, which makes it a potential target for this disease[37]. It has been proposed that specific genetic components contribute to the development of hypertension. Such is the case of the NKCC1, a sodium-potassium-2 chlorine cotransporter that is implicated in ion transport and is significantly present in the aortic tissues; overactivity of this ion transporter in the aorta may result in hypertension [38]. In addition, researchers observed that hypomethylation of NKCC1 promoter was evident with increased NKCC1 expression in the heart and aorta of spontaneously hypertensive rats[39] and this phenomenon appears to develop with the postnatal changes of hypertension in the relevant model[40]. On the other hand, there is strong evidence of prominent hypomethylation of the norepinephrine transporter (NET) in populations with essential hypertension. NET is a prominent sodium chloride-dependent transporter that regulates Norepinephrine concentration within the body[23]. Additionally, some evidence has linked hypomethylation of a specific gene, body Glucokinase (GCK), to essential hypertension. [27, 41]

Genome-wide DNA methylation analysis is essential in determining the methylation status of either the promoter or the non-promoter CpG sites associated with hypertension (HTN). Recent research claims that the levels of 5-methylcytosine, i.e. 5mC, are much lower in people suffering from essential hypertension compared to non-affected populations[23]. On the other hand, some women suffering from pre-eclampsia,

which is when women are pregnant but are also suffering from hypertension, have amplified overall cellular methylation of DNA[27,42]. Most notably, the analysis showed that the sulfatase 1 (SULF1) gene is profoundly hypermethylated in hypertensive patients. In contrast, the ATP-binding cassette G4 (ABCG4) gene was markedly demethylated in the population of hypertensive patients. These discoveries emphasise the plausibility that ABCG4 gene methylation is instrumental in the pathogenesis of hypertension[23].

Various factors that lead to HTN pathogenesis, such as age, gender, smoking, nutrition, alcohol consumption and obesity, were presumed to be associated with DNA methylation changes. However, few studies aim to investigate the influence of these factors on the methylation status in HTN[23]. For example, an interaction between alcohol consumption and ADD 1 promoter methylation was shown to influence EH risk[23].

It has been postulated that these different responses to antihypertensive treatment among patients carrying the same b1 adrenergic receptor (b1-AR) gene polymorphisms are due to changes in DNA methylation. DNA methylation may affect antihypertensive drugs' efficacy and contribute to individuals' heterogeneity [44].

We examined the methylation status of the KLOTHO and ARNTL genes in 78 hypertensive subjects and 49 controls using methylation-sensitive high-resolution melting (MSHRM). Our analysis found no significant association between KLOTHO and ARNTL methylation and the hypertensive phenotype, nor with fasting blood sugar, triglycerides, cholesterol levels, sodium, creatinine, potassium, or urea in hypertensive patients. However, we did find a significant difference in potassium levels between hypertensive patients with methylated KLOTHO and control subjects with unmethylated KLOTHO[21].

Table 1. The list of gene-specific and genome-wide DNA methylation in the context of HTN

Gene	DNA methylation	Effects	Subjects	Reference
CORIN	Hypermethylation	Lower probability of prevalent HTN	Human peripheral blood mononuclear cells	44
ACEII, SCNN1B, CKG, IFN-γ	Hypermethylation	HTN risk	Meta-analysis	45
TLR2, IFN-γ, ADD1, AGTR1, GCK	Hypomethylation	HTN risk	Meta-analysis	45
AT1aR	Hypomethylation	HTN risk	Age-matched SHRs and WKY rats	26
AT1a	Hypomethylation	HTN risk	Offsprings of pregnant rats with nicotine exposure	28
AT1b	Hypomethylation	HTN risk	Offsprings of pregnant rats with low protein diet	29
AT1b	Hypomethylation	HTN risk	Virgin female Wistar rats	30
ACE	Hypomethylation	HTN risk	Maternal low protein diet in fetal rats	31
ACE	Hypomethylation	HTN risk	Low-birth weight children	32
ECE-1c	Hypermethylation	Regulator for HTN	Vascular endothelial cells	33
ADD1	Hypomethylation	HTN risk	Essential hypertensive patients	36

Gene	DNA methylation	Effects	Subjects	Reference
11bHSD2	Hypermethylation	HTN risk	Essential hypertensive patients	37
NKCC1	Hypomethylation	HTN risk	SHRs	39 40
NET	Hypermethylation	HTN risk	Essentail hypertensive patients	23
GCK	Hypomethylation (Gene-body methylation status)	HTN risk	Essentail hypertensive patients	41
SULF1 GWS)	Hypermethylation (Non-CpG island)	HTN risk	Hypertensive patients	46
ABCG4 (GWS)	Hypomethylation	HTN risk	Hypertensive patients	47

CONCLUSION

High blood pressure, also known as hypertension (HTN), is a long-term condition influenced by both genetic and environmental factors. It significantly increases the risk of developing kidney and cardiovascular diseases [1,2]. Although cardiovascular disease (CVD) has traditionally been associated with older age groups[3,48,49], its incidence is rising among children and adolescents. The main factors that contribute to the development and progression of HTN include age, sex, genetics, lack of physical activity, high salt and alcohol consumption, obesity, and diabetes mellitus[5].

Previously, researchers have gradually focused on different targets, including circular RNA, and metabolites, which could be used as potential prognostic markers, diagnostic tools, and therapeutic targets for hypertension (HTN). It also highlights the importance of DNA methylation-based biological age metrics, which are integral in identifying epigenetic targets that can be pivotal for HTN. Thus, combining blood pressure measurements with biological age estimates based on DNA methylation can improve the prediction of HTN[50].

As shown in Table 1, many studies have focused on DNA methylation of genes involved in hypertension (HTN). The novelty of our research lies in exploring, for the first time based on preliminary evidence, the influence of KL and BMAL1 gene promoter methylation on HTN. Although KL and BMAL1 genes have been linked to HTN, no previous studies have investigated their promoter methylation in this context. Additionally, research indicates that the circadian rhythm of blood pressure (BP) is often disrupted with age[51]. Interestingly, nitric oxide administration has been suggested to restore BP circadian variation disrupted by aging[52]. Hypertension (HTN) is a complex disease, requiring future studies to include genome-wide methylation data to better understand the specific DNA methylation mechanisms involved in its onset and progression. Moreover, biological age does not always align with chronological age. Evidence suggests that individuals with higher biological ages are more likely to develop HTN later in life. Therefore, incorporating DNA methylation-based biological age measures into future research could support early intervention strategies for HTN and help develop personalised prevention approaches.

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Authors's contribution:

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