

Review Article

The Genetic Basis of Hypertension: An Overview

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Abstract

In light of the widespread recognition of the heritability of hypertension (HTN), numerous studies have been conducted to better understand the pathogenesis of different variants of HTN and their interactions. The complexity of crucial HTN makes it difficult to segregate and identify particular genes that influence blood pressure (BP) fluctuation, making the development of single-gene targeted treatments tough. Therefore, finding HTN susceptibility genes will contribute to the understanding of the biology behind the disease. Apart from its potential impact on antihypertensive drug therapy selection, genomic information may also contribute to identifying persons at risk of developing the condition, resulting in new preventative strategies. It is necessary to conduct more replication studies in other populations to confirm that there is a link between certain genetic variations and the varying response to these frequently used antihypertensive medications. Moreover, antihypertensive medication responsiveness to epigenetics and regulatory networks may be improved by further research. This may aid researchers to find new HTN therapeutic targets. This study aimed to come up with a list of known genetic variants that may play a role in HTN.

Keywords: Hypertension, Genetics, Epigenetics, Pharmacogenomics, Heredity, Antihypertensive medications, Therapeutic targets

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Introduction

Hypertension (HTN) is one of the most prominent causes of global mortality and morbidity as well as a key modifiable risk factor for renal, cardiovascular, and cerebrovascular diseases (1). Increased development in the medical field has fueled the understanding of blood pressure's (BP's) complicated pathophysiology, where hereditary and external factors interact with a myriad of biological reactions and mechanisms to produce the phenotype. However, while observational studies have advanced our understanding of external factors that affect BP, particularly nutrition and lifestyle, distinguishing the precise role of heritability in this set-up from the shared environment observed in families and communities was proven to be difficult (2). The medical implications of determining the genetic variables that furnish BP (BP) fluctuations and antihypertensive drug responsiveness are considerable. Knowing whether or not a person is predisposed to the heritability of HTN can lead to the early implementation of preventative measures and the design of effective treatment programs. Furthermore, pharmacogenomic data can contribute to the development

of individualized pharmaceutical regimens, which can improve therapeutic responses while lowering healthcare expenditures at the same time (3).

Having high BP is a significant health problem for kids and adults. More than a third of adults in the United States were said to have HTN between 2009-2012. (4). People between the ages of 3 and 18 who have high BP are more likely to suffer from high BP (5). Adults still face a lot of problems and deaths because of high BP. HTN is thought to be responsible for about 45% of morbidity from cardiovascular diseases and 51% of morbidity from strokes (6). Although it is very common, the cause of essential HTN is still mostly unknown. There is more evidence that HTN is caused by a complicated mix of epigenetic, genetic, and environmental factors. Genetic materials were found to play a role in about 30%–60% of BP variations (6,7). However, only 3% of BP variations can be explained by known genetic factors. This shows that many genetic variants have not yet been found (8).

Methods and Materials

To obtain the essential information, several published



research and review articles were downloaded from Google Scholar, ScienceDirect, PubMed, Research Gate, and other web sources.

Hypertension and Genetic Linkage

Several genetic variations have been linked with an increased risk of HTN in genetic epidemiology research (9). The heritability of this complicated condition is most likely due to a combination of genes in lieu of a single gene. Various studies on the genetics of HTN yielded complicated, inconsistent, and non-reproducible data, making it impossible to draw an association between individual genes and HTN (Table 1) (10). Angiotensinogen (AGT) was the first candidate gene causing essential HTN, and it is still the “most examined” gene connected with the disease (11). It is found in a variety of tissues, including the liver, heart, vascular wall, adipose tissue, brain, and kidney, and its cell specificity is similarly diverse. The renal proximal tubule epithelial cells, liver hepatocytes, adipocytes in fat, astrocytes, and selected neurons in the brain are all cell types that express AGT. The human AGT gene, which belongs to the serpin gene family, is only 12 kb long and has 5 exons on chromosome 1 (1q42-q43) (starts with nucleotide 227 156 602 on chromosome 1). It has homologs in vertebrates and is highly preserved in vertebrates (12). The promoter is located in the 1.2-kb region directly upstream of the first exon, while an enhancer is located in the 3' flanking regions immediately downstream of the second polyadenylation site (13). Although this enhancer generates a 40-fold elevation of expression in human hepatocyte cell lines when reporter constructs are used, its relevance in vivo has been questioned (14). A signal peptide is eliminated co-translationally from the 485 amino acid (61 kDa) human AGT glycoprotein to yield the 452 amino acid renin (REN) substrates. While AGT is released continuously, new research reveals that it may also be found in the nucleus of some cells (15).

Epigenetics of Hypertension

Epigenetic phenomena include histone modification after translation, methylation of DNA, and non-coding microRNAs (miRNAs) and are associated with fluctuations in the expression of genes even though there are not changes in the DNA itself (16). Epigenetic changes

can be passed down through the generations, but they can also be changed by food, drugs, prenatal care, and other factors. They may also be reversible. Since they ensure that only specific genes are expressed in specific cell types, epigenetic events are critical for processes such as cell development and cell differentiation (6). HTN can be caused by abnormalities in epigenetic processes, and it has been connected to numerous epigenetic problems as detailed below (17).

Histone Modification

Alteration to the N-terminal tails of histone proteins (e.g., methylation and acetylation) can cause changes in the dynamics of the chromatin structure and function. As a result, gene expression is either reduced or boosted (18). Histone alterations and HTN have been linked to both animal and human studies. According to one study, histone alterations caused angiotensin-converting enzyme 1 (ACE1) overexpression in hypertensive rats' organs (19). Cell-specific histone alterations were discovered to influence the amounts of messenger RNA (mRNA) for endothelial nitric-oxide synthase in human endothelial cells. Endothelial nitric-oxide regulates BP by altering vascular tone via nitric oxide synthesis in the vascular endothelium (20,21).

DNA Methylation

Cytosine-guanine dinucleotide sequences are the places where DNA methylation happens. When a methyl group is covalently bound to cytosine, the result is 5-methylcytosine (7). DNA methylation of cytosine-guanine dinucleotides, which are often found in promoter regions, slows down transcription and stops genes from being turned on (18). In some studies, the level of DNA methylation has been linked to how quickly and severely HTN starts and how long it lasts (22).

Non-coding RNAs (ncRNAs)

NcRNAs are becoming more well-known as important modulators of genetical expression, with the potential to impact cell specificity of gene expression (16). MiRNAs have been the most extensively researched non-coding RNAs as they are tiny non-coding RNAs with the size of around 22 nucleotides that mute mRNA expression by preventing mRNA breakdown or interfering with mRNA translation (23). MiRNAs have been shown to influence BP through a variety of methods. The REN-angiotensin system route is one such mechanism. By attaching to their 3' untranslated regions, hsa-miR-663 was shown to modulate the mRNA levels of REN and apolipoprotein E in human kidneys (24). Furthermore, hsa-miR-181a has been shown to have an effect on the mRNA expression of REN and mitochondrion-associated 1 AIFM1. In HTN, both miRNAs were significantly suppressed, which led to an increase in REN mRNA expression (24).

Table 1. Different Types of Genetic Hypertension

Monogenic Form of Hypertension	Polygenic Form of Hypertension
Liddle's syndrome	RAA system
Abnormal mineralocorticoid excess	G-proteins/signal transduction pathway
Glucocorticoid-remediable aldosteronism	Noradrenergic system
Activating mutation in the MR	Ion channels
Type II pseudo hypo-aldosteronism	Immune system and inflammation

Note. RAA: Renin-angiotensin-aldosterone; MR: Mineralocorticoid receptor.

Studies on Hypertension Genetics

Monogenic Form of Hypertension

In Mendelian or monogenic variants of HTN, the regulation of salt reabsorption in the kidney is affected, indicating that this organ plays an important part in the etiology of HTN. Evidence obtained from empirical studies suggests that active participation of the kidney plays an important role in the persistence of HTN (25). Furthermore, substantial increases in BP have been documented in humans, primates, and rats in response to increasing dietary salt intake, demonstrating how genetic fluctuation can affect the salt management in the kidney (26,27). The link between genetic variation and monogenic forms of HTN sheds light on the most frequent kind of HTN, particularly in patients with a known genetic abnormality. The T594M mutation of the epithelial sodium channel (ENaC), for example, has been linked to HTN in Black individuals, while polymorphisms in aldosterone synthase have been associated with essential HTN (Figure 1)(28,29).

Liddle's Syndrome

It is an autosomal dominant condition characterized by the rise in the salt and water resorption level in the collecting tubules of the kidneys, resulting in HTN. Mutations in the ENaC β and γ subunit genes were revealed to be the cause of the disease (30).

Abnormal Mineralocorticoid Excess (AME)

Moderate to severe HTN appears at an early age in patients with AME, which is caused by an autosomal recessive disease. A deficiency in 11 β -hydroxysteroid dehydrogenase, which results in cortisol inactivation, was found in patients with AME1, but enzymatic activity decreased in patients with AME2 due to a distinct mutation in the same gene found in patients with AME1 (31).

Glucocorticoid-Remediable Aldosteronism

It is generated by a duplication of the aldosterone synthase and 11 β -hydroxylase genes due to an uneven crossing. As a consequence, elevated levels of aldosterone are produced,

which is regulated by an adrenocorticotrophic hormone. This results in increased salt and water resorption as well as an increase in BP (32).

Activating Mutation in the Mineralocorticoid Receptor (MR)

810 (S810L) mutation in the MR is an activating mutation that causes early-onset HTN aggravated during pregnancy. This mutation changes receptor specificity and causes constitutive MR activity (33). When attached to the wild-type MR, the mutant receptor (L810) is activated by chemicals including progesterone which has an inhibitory action on the wild-type receptor (32).

Type II Pseudohypoaldosteronism

Pseudohypoaldosteronism type II is an autosomal dominant illness that causes hyperkalemia, critical HTN, and thiazide diuretic sensitivity (34). This is related to changes in the way Na-Cl and K are managed. The condition is caused by mutations in two members of the WNK kinase family: WNK1 and WNK4. In the kidney, both genes are strongly expressed (35).

Polygenic (Essential) Form of Hypertension

Renin-Angiotensin-Aldosterone (RAA) System

In terms of genetic vulnerability to HTN, the RAA system is one of the most thoroughly investigated systems. Various components of this system have been explored. In this group, the AGT gene has consistently shown positive outcomes so far. AGT molecular variations predispose to HTN according to sib-pair linkage analysis (36). A latest analytical review found a link between the substitution of methionine for threonine at position 235 (M235T) and an elevated risk of HTN (37). This gene may have a varied role in various ethnic backgrounds, with a positive correlation in White people but not in Black or Asian people (38). An Australian Anglo-Celtic Caucasian study, on the other hand, indicated that the AGT gene did not make a contribution to the pathogenesis of HTN in this population (39). A relationship between the AGT locus and HTN was discovered in a linkage analytical research

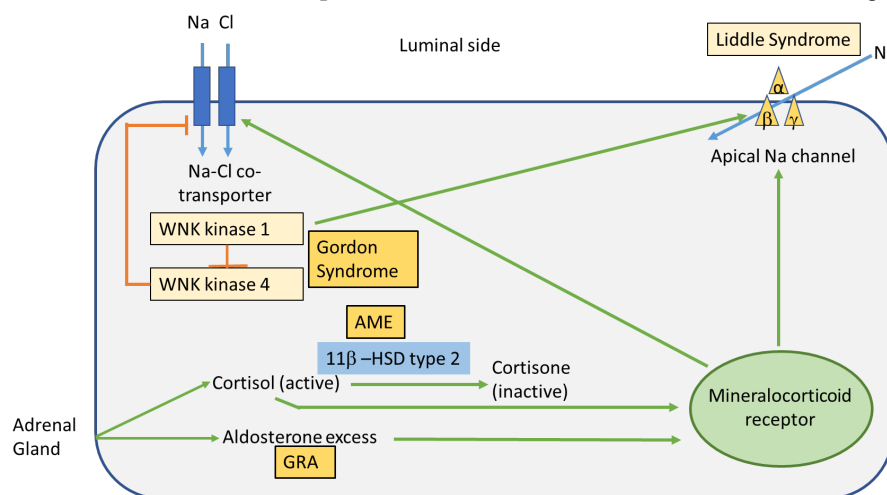


Figure 1. Different Molecular Pathways in Monogenic Hypertension .

utilizing the affected-pedigree-member approach, however, no link to M235 T was discovered (40).

Signal Transduction Route System Involving G-proteins and Hormones

Hormones and neurotransmitters modulate these signaling pathways, which in turn affect BP. In the case of the G-protein signaling regulator (i.e., RGS2), it has a preference for the Gαq subclass of G-proteins, which is associated with various cardiac hormones such as angiotensin II, thromboxane A, endothelin I, and norepinephrine. (41).

G-protein subunit gene polymorphisms are likely to have a considerable impact on the cardiovascular system. As a result, examining the genetic polymorphisms of the system's components may provide a fresh perception of the pathogenesis of HTN and may lead to the discovery of novel targets for treatment. The β3 component of the G-protein gene (GNB3) polymorphism was thought to be a promising option for studying cardiovascular pharmacogenetics (42). GNB3 has a new variant (i.e., C825T) that has been associated with an increased risk of HTN (43). There was a relationship between 825T allele and HTN in Whites in a study (44). As a result, thiazide diuretics have a stronger effect on bearers of the 825T allele. According to another study, the G protein β3 subunit gene C825T polymorphism was linked to HTN in males in a large-scale association analysis conducted on Japanese people (32).

Noradrenergic System

Three polymorphisms in the β2-receptor were examined in the noradrenergic system. The findings from different ethnic groups are mixed, implying that more research is needed to be conducted on the processes by which these polymorphisms affect BP variances (45). Genome-wide linkage analysis identified a similar relationship between HTN, 16Gly, and 27Glu/Gln (46). However, research on Japan's population found that these single-nucleotide polymorphisms (SNPs) were not linked to HTN (47). These polymorphisms were not found to have a significant connection with essential HTN in haplotype studies (48).

Ion Channels

In investigations on Liddle's syndrome, ENaC was discovered to be a plausible potential target for severe HTN, and it is now being further investigated. The T594M mutation in the β subunit of this gene increases the likelihood of developing HTN in African-Americans (28). This gene, on the other hand, has just a tiny impact on BP in Japanese people (49). Using a sibling-pair study of White individuals, it was discovered that there is a relationship between high systolic BP and microsatellite markers on chromosome 16p12.3 near the ENaC β and γ subunit genes (50). SCNN1A, SCNN1B, and SCNN1G, which code for amiloride-sensitive sodium channels, were also examined. The SCNN1A G2139 allele was

demonstrated to enhance the risk of HTN, while SCNN1b and SCNN1G were implicated in the etiology of systolic BP (SBP) according to a sib-pair linkage study (50).

Immune System and Inflammation

For the past several years, researchers have been looking at the immune system components that may be involved in the genesis of high BP. The existence of a relationship between these components and HTN has only been discovered in a few research. Several studies, such as those on the relationship between nitric oxide synthase (NOS3) gene polymorphisms and HTN, have stirred controversy. In Polish people, there was no substantial link between the G11T mutation, NOS3 gene, and HTN (51). A variation in the NOS3 gene, on the other hand, has been associated with essential HTN and may therefore serve as a genetic diagnostic for essential HTN in Japanese people (52). A latest study discovered a substantial relationship between a polymorphism in the NOS3 gene and SBP level (53).

Hypertension and Pharmacogenomics

Pharmacogenomics is the study of genes that have an impact on a patient's reaction to therapy. Drug response to medication is determined by genetic factors, and the purpose of pharmacogenomics is to provide patients with individually customized treatments and doses that consider these variances. The genetic component of antihypertensive medication responses, which includes chemical interaction with targeted cells, drug transportation, and degradation, is becoming increasingly recognized. Since its inception in 2009, the Clinical Pharmacogenetics Implementation Consortium has been working to produce guidelines to help with the translation of pharmacogenetic data into actionable pharmaceutical prescriptions for patients (54). In contrast, there are currently no Clinical Pharmacogenetics Implementation Consortium guidelines for antihypertensive medicines due to contradictory findings across trials and, as a result, evidence is inadequate to provide recommendations (55,56).

The International Consortium for Hypertension Pharmacogenomics Studies (<http://icaps-htn.org>) was founded in 2012 to promote research into genetic variations that cause interpatient heterogeneity in antihypertensive drug reactions. Beta blockers and thiazide diuretics have provided the most consistently repeatable pharmacogenomic data to date (57). ADRB1, NEDD4L, and YEATS4 have all been consistently associated with antihypertensive medication responses in numerous studies. The ADRB1 gene codes for one type of adrenergic receptor, which is the target of blockers. Ser49Gly (rs1801252) and Arg389Gly (rs1801253) are two common SNPs in the ADRB1 gene (58). Patients who were homozygous for Arg389 and had the Ser49Arg389/Ser49Arg389 diplotype exhibited a higher drop in BP with metoprolol than those who were Gly allele carriers and had the Gly49Arg389/Ser49Gly389 diplotype, respectively (59,60).

NEDD4L is a protein that regulates sodium reabsorption in the kidneys by inhibiting ENaC expression in the distal nephron (61). Several studies have attributed the G allele of the rs4149601 gene, which is found inside the NEDD4L gene, to a larger reduction in systolic and diastolic BP in response to thiazide diuretics (62,63). The involvement of NEDD4L in decreasing tubular sodium reabsorption is supported by these findings.

Pharmacogenomics-Based Antihypertensive Medications

The risk of adverse cardiovascular events and BP reduction associated with the use of currently available antihypertensive drugs is highly variable between individuals with little understanding of the underlying mechanisms and just a few reliable predictors (64). In the field of pharmacogenetics, the goal is to discover genetic indicators for drug responsiveness and adverse effects that can be used in medical care before commencing treatment (65). It is possible to explain variability in drug response amongst people by looking at the quantity of drug that hits its targets (pharmacokinetics) or the changes in response caused by drug-receptor interactions (pharmacodynamics) (65). Pharmacokinetics, and accordingly, drug responsiveness and toxicity may be affected by genetic variations altering absorption, distribution, metabolism, and excretion. In addition, genetic variations that make it hard for drugs to interact with receptors or send signals inside the body could make pharmacodynamics and pharmacological effectiveness different (65). People who take antihypertensive medicines in the real world, such as diuretics, ACE inhibitors, angiotensin II receptor blockers (ARB), beta-blockers, and calcium channel blockers have different genes that make them more likely to be hypertensive, and this is called pharmacogenetics (Table 2) (65).

Diuretics

Thiazide diuretics are the most commonly prescribed class of diuretics, and hydrochlorothiazide (HCTZ) has been the subject of the majority of diuretic pharmacogenetic investigations. When SNPs were found in or near the genes YEATS4 (YEATS domain containing 4), PRKCA (protein kinase C, alpha), and NEDD4L, the connection between HCTZ response and SNPs was proved to be moderate (Level 2B). Diastolic blood pressure (DBP) response to HCTZ was investigated in a genome-wide association study in Blacks, and researchers discovered a region on chromosome 12q that was related to a response. According to the results of the haplotype analysis, HCTZ response was associated with SNPs near the genes YEATS4, LYZ, and FRS2 on chromosome 12q. Black good responders were more likely to have the ATC haplotype than Black poor responders ($P = 0.0002$), whereas Black poor responders were more likely to have the ACT and ATT haplotypes (both $P = 0.0018$). In this study, the SNP rs7297610 was found to have the highest individual significance ($P = 0.00036$), and it was found to

Table 2. Significance of Various Types of Pharmacogenomics-based Anti-hypertensive Drugs

Types of Medicine	Significant Effects	Reference
Diuretics	Modulate diastolic BP through SNPs in the region YEATS4 and LYZ	66
ACE inhibitors and angiotensin II receptor blockers	Act on the RAAS	67
Beta blockers	Dose adjustment may impact systolic BP	74
Calcium channel antagonists	Randomly treating with verapamil can increase risk	76

Note. BP: Blood pressure; SNPs: Single-nucleotide polymorphisms; ACE: Angiotensin-converting enzyme; RAAS: Renin-angiotensin-aldosterone system.

be responsible for the majority of the observed connection. They were confirmed in a different group of 291 Black and 294 White individuals, demonstrating that the area between the genes YEATS4 and LYZ is related to DBP response in both races (66).

ARB and ACE Inhibitors

In the treatment of HTN, ACE inhibitors and ARB are the first-line medications. A three-year prospective Chinese study investigated benazepril's BP response. In this study, they looked at 14 SNPs in the genes AGT, AGTR1 (angiotensin II receptor, type 1), and AGTR2 (angiotensin II receptor, type 2). In the general population, this variable was responsible for 9.6% of the difference in DBP. However, there was no link between AGTR1 or AGTR2 SNPs and health. It was the GAG haplotype that was cut down on SBP more than the GAC haplotype or the group that did not have both GAG and GAC haplotype (e.g., rs1403543, rs5194, and G3726). According to the study, the AGTR1 haplotype is to account for 13% of the systolic and 9.6% of the DBP drops.

After three months of losartan medication, hypertensive patients with the CYP2C9*1/*30 genotype displayed poor results in BP reduction (68). CYP2C9 catalyzes the oxidation of losartan to a more powerful metabolite, signaling that the *30 allele has lower activity, which may contribute to the poor response to losartan (65).

Beta-Blockers

The Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association has looked at how the CYP2D6 genotype affects how much metoprolol should be used to treat people. Since metoprolol is mostly broken down by CYP2D6, they said people who have at least one inactive or two less active alleles should either switch to another drug or cut back on their dose. They said that ultra-fast metabolizers should have their doses changed (69). Studies say that metoprolol should not be changed to meet BP targets, but other studies say that it should be changed (70,71).

Additionally, a study found that patients with the Ser49/Arg389 haplotype had a higher death rate when given verapamil but not atenolol (72). These two SNPs

strongly suggest that beta-agonist-induced intracellular signaling has functional consequences (73). Patients with essential HTN treated with atenolol were found to have higher systolic blood pressure responses when they carried the wild type allele and haplotype of the GNB3 A3882C, G5249A, and C825T polymorphisms according to the findings of a pharmacogenetic study conducted on essential HTN patients (G-protein beta3 subunit). Furthermore, when adjusting for gender, the correlation remained significant in females but not in males. It was also revealed in the same study that there was no correlation between the ADRB1 and ADRB2 polymorphisms in either gender (74).

Calcium Channel Antagonists

In a study using samples from International Verapamil SR-Trandolapril Study (INVEST) patients, the Glu65Lys and Val110Leu genotypes of KCNMB1 (potassium large conductance calcium-activated channel, subfamily M, and beta member 1) did not affect the BP response to verapamil. Carriers of Leu110, on the other hand, had a decreased risk of the primary outcome (all-cause death, nonfatal myocardial infarction, or nonfatal stroke) (75). Another study published in INVEST evaluated eight SNPs in the CACNA1C coding area and intron-exon junctions. There was no correlation between the tested polymorphisms and the primary influence on the outcome; however, there was a significant interaction between rs1051375 and the treatment method. When patients were assigned to verapamil SR or atenolol in the INVEST-genes cohort, the AA genotype for the SNP rs1051375 was identified, which led to a 45% reduction in the risk of the primary in the study. The primary outcome was much more common in GG genotype (GG) people randomly assigned to verapamil SR than in GG people randomly assigned to atenolol, with a 4.5-fold increased chance of developing the primary outcome. Furthermore, heart tissue CACNA1C allelic mRNA expression was comparable amongst genotypes in terms of expression in cardiac tissues (76).

Conclusion

HTN is produced by a complex combination of hereditary, epigenetic, and environmental variables that all interact. People with high BP cannot separate single, specific genetic traits that make them more likely to experience the condition. Despite this, new gene mutations and epigenetic mechanisms that play a role in BP variability are still being found, which helps us learn more about how BP is controlled and how HTN is passed down through the generations. Inter-patient variation on how antihypertensive medications work is well-known, and pharmacogenomics could help people get better results from their antihypertensive drugs by giving them personalized regimens that work better for them. Continued research is needed to find more genes, variants, genomic, and regulatory pathways that influence how antihypertensive medications operate.

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Authors' Contribution

MSA has conceived the original idea. FY, ArS, and AnS prepared the initial manuscript with referencing. JAC, AAC, TA, and SK critically reviewed the overall activities. FA have supervised the whole manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interests

The authors have no conflict of interest to disclose.

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