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Review Article

A Mini Review of Gene Polymorphisms in the Renin-Angiotensin System Linked with Primary Hypertension

Mais Yousif[1], Eyas Alkhayer[2], Haitham yazigi[3], Faisal Redwan[4]

[1,3,4]*Department of Laboratory Medicine, Faculty of Medicine, Tishreen University, Latakia, Syria.*
[2] *Department of Cardiac Internal Diseases, Faculty of Medicine, Tishreen University, Latakia, Syria.*

[1]*Corresponding Author : maisjyousif@hotmail.com*

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Abstract *- Hypertension is considered a global health problem due to its rapid spread in all advanced and developing countries. It is considered the main cause of global deaths and cases of disability, as cardiovascular diseases develop in patients despite receiving treatment, which indicates the failure of the antihypertensives used to ensure ideal control of blood pressure. The decrease in the effectiveness of treatments and the variation in response to them could be related to genetic variation between individuals, and this was demonstrated by the increased probability of developing high blood pressure in the event that the patient has a family history, as the genetic cause constitutes 25-60% of cases, and the analyzes that showed A study conducted at the whole genome level found 118 genetic loci associated with blood pressure, as well as several genetic polymorphisms that may affect protein synthesis and cause the development of the disease.*

The goal of this review was to look into the molecular base of hypertension by studying the genes that organize the renin-angiotensin-aldosterone pathway, which is implicated in the evolution of primary hypertension, and focus on the clinical and pathological features resulting from the associated genetic polymorphisms. The study of the molecular ground of primary hypertension may be useful in the future in developing the most effective and safe individual treatments for each patient according to his genetic fingerprint and avoiding experimental treatments. This review is distinguished by its reliance on the latest research recently published research and books on the mechanisms and genetics of high blood pressure and RAAS pathway.

Keywords *- Renin-angiotensin system, Primary hypertension, RAAS genes, SNPs, Polymorphisms.*

1. Introduction

Recent years have witnessed great developments in molecular medicine and genetic engineering techniques that have been used to improve the treatment and control of clinical diseases.

The Human Genome Project has also been completed, which was considered one of the most important and greatest scientific achievements during the twenty-first century, and whose goal was to goal develop a detailed map of the genetic material in humans by knowing the sequence of deoxyribonucleic acid (DNA), allowing the analysis of each individual's genome to be carried out in light of this, and developing an individual genetic map for each patient that shows the various current and future genetic characteristics, both healthy and sick, are clarified with different degrees of probability, thus arriving at the molecular basis of common genetic diseases such as cardiovascular disease, high blood pressure, and cancer This discovery constituted the gateway to a new era of digital biology. [1]

After the human genome sequencing experiment, a new approach was turned to called the individualization of drug treatment, with the development of what is called individualized (personalized) medicine, which aimed to abandon the idea that patients with a specific disease are subject to a specific treatment plan and show the same responses when they receive the same drug according to The dosage system itself, and its purpose was to personalize the treatments, as the appropriate treatment plan is designed for each patient and the appropriate medications, dose, and administration time are selected for him and not for others, according to his genetic fingerprint, environmental conditions, and lifestyle patterns, so that the treatment targets the main axis causing the disease in him. The patient is spared experimental co-treatments that may cause him many side effects, which enables us to reach the maximum possible levels of effectiveness and safety in clinical practice. [2]

Genetic mutations and single-nucleotide polymorphisms that may occur in genes regulating various pathways in the body play a major role in causing hereditary diseases and contribute to causing variation in the therapeutic response of patients to the same classes of drugs. This may be due to the effectiveness of drugs being affected by the interactions that may occur between the drugs and the

gene, as well as the effects of genotype on the enzymes responsible for drug metabolism, those responsible for drug transport and which participate in complex metabolic reactions.[3]

Hypertension (HTN) is deemed one of the most prominent genetic diseases that represent the utmost challenge at the public health level. According to the newest World Health Organization statistics for the year 2021, it is estimated that 1.28 billion adults around the world suffer from HTN, and two-thirds of them live in middle- and low-income countries.[4]

Epidemiological studies show the prevalence rate is constantly increasing, and the number of infected people is expected to reach approximately 1.5 billion by 2025. The global prevalence rate in adults has ranged between 30% and 45%, and it affects more than 60% of individuals aged 60 years and over.

Above, one of the most prominent objectives of the global community in the context of the Development targets was to lower the widespread presence of HTN by 33% by 2030 [7, 8]; this disease constitutes a universal epidemic whose proportions are still unknown.

It often develops asymptomatically and is first diagnosed when one of its complications occurs, such as myocardial infarction or stroke; therefore, it is alluded to as the “silent killer”. [4]

The study of the international burden of HTN, organized by the World Health Organization, began in 2003, as it is the main cause of Cardiovascular Disease (CVD) and the fatal events resulting from it in its various forms, including (coronary artery disease, myocardial infarction, heart failure, left ventricular hypertrophy, Fatty heart disease, cardiac arrhythmias including atrial fibrillation, in addition to ischemic and hemorrhagic cerebrovascular accidents, peripheral arterial disease, sudden death, and renal disease), and this alliance has been confirmed through studies conducted on variable age and ethnic groups, as it causes more than 10 million deaths and 218 million disability-adjusted lives, thus forming a vast financial burden on the health care system. [4]

Blood Pressure (BP) is regulated by several systems, including renin Angiotensin Aldosterone System (RAAS), Sodium system, Natriuretic peptides, Signal transduction pathways, Noradrenergic system, Endothelin system, Adducin, Apolipoproteins, Cytokines, Neuropeptide Y. Among these systems, RAAS is considered the most important, given the vital role that the RAAS plays in regulating blood pressure, and considering that the drugs that target this pathway are the initial line used in the therapeutic management of hypertension. [5]

This review highlights the crucial role of genetic and epigenetic etiologies in the pathogenesis of primary hypertension and the role of Renin Angiotensin Aldosterone System (RAAS) and its polymorphisms in the genes encoding its components, which are linked to hypertension and many other disorders.

2. The Renin Angiotensin Aldosterone System (RAAS)

This system is considered the most important among the nervous and hormonal systems regulating blood pressure, as it widely affects the pressure of blood and controls sodium retention based on renal perfusion pressure. RAAS consists of the following components.

2.1. Angiotensinogen (AGT)

It is a human plasma glycoprotein that is diverse in character and consists of 452 amino acids, and it represents the main substrate of the RAAS system, through sequential divisions to form many angiotensin peptides.

The liver is considered the major source of manufacturing of this compound. It is also produced locally by multiple resources such as ovaries, kidneys, adrenals, brain and heart. It contributes to controlling arterial pressure, as AGT undergoes a change after its interaction with an enzyme called renin. Long-term elevation of plasma levels of angiotensinogen constitutes a risk factor for developing HTN. [6]

2.2. Renin

Renin secretion is the starting point for RAAS activation, and it is produced mainly by special cells located next to the glomeruli inside the kidneys. Several mechanisms participate in stimulating the secretion of active renin, the most important of which are renal perfusion pressure, the degree the sympathetic nervous system activity, and the amount of sodium sensed by the macula densa cells in the kidneys. Renin biosynthesis occurs from the prorenin by removing 43 amino acids from the terminal end of this precursor compound. This Mature form of renin is kept in stored granules in the juxtaglomerular cells of the kidneys to be emmision to the blood when needed.

Renin plays the role of an aspartyl protease enzyme, as it acts on angiotensinogen to cleavage the bond at the N-terminal end, producing a biologically inactive deca-protein called angiotensin I.

Despite the promising progress in developing modern and more effective antihypertensive agents, the renin inhibitors that have been developed so far have not shown good efficacy compared to other drugs that target the Ras pathway, and it was necessary to use combination therapy by sharing these inhibitors with other antihypertensive drugs to reach to the desired effect. [5]

2.3. Angiotensin-Converting Enzyme (ACE)

It is a mineral enzyme that works to make a structural modification to the angiotensin I compound by cutting the peptide bond between histidine and His-Leu at the C-terminal side. This is done in many organs, especially in the lungs and the endothelial cells of the blood vessels Activation of the previous compound results in the formation of another biologically active compound. It is called angiotensin II (Ang II), which is deemed to be one of the strongest and most violent vasoconstrictors in the body. Moreover, ACE also stops the effectiveness of some substances that have a vasodilating effect, such as bradykinin.[7]

In the year 2000, a new enzyme was found that is very similar to ACE and is and is symbolized by ACE2, which also be the property of the same family of metalloproteinases and exists in one of two forms, as it may take either the form associated with cell membranes or the soluble form that is soluble in the blood. The enzyme works to inhibit the work of the traditional RAAS pathway through changing Ang II to another protein called angiotensin (1-7), which contributes to local vasodilation and lowers arterial pressure. [7]

2.4. Angiotensins

Angiotensins are biochemicals that are differentiated by their amino acid content. They result in enzymatic hydrolysis of angiotensin 1 into various angiotensin peptides. Each of these compounds has a special function and is symbolized by (Ang) followed by a number specific to each. Figure 1 shows the different types of angiotensin compounds and the mechanism of their formation. [5]

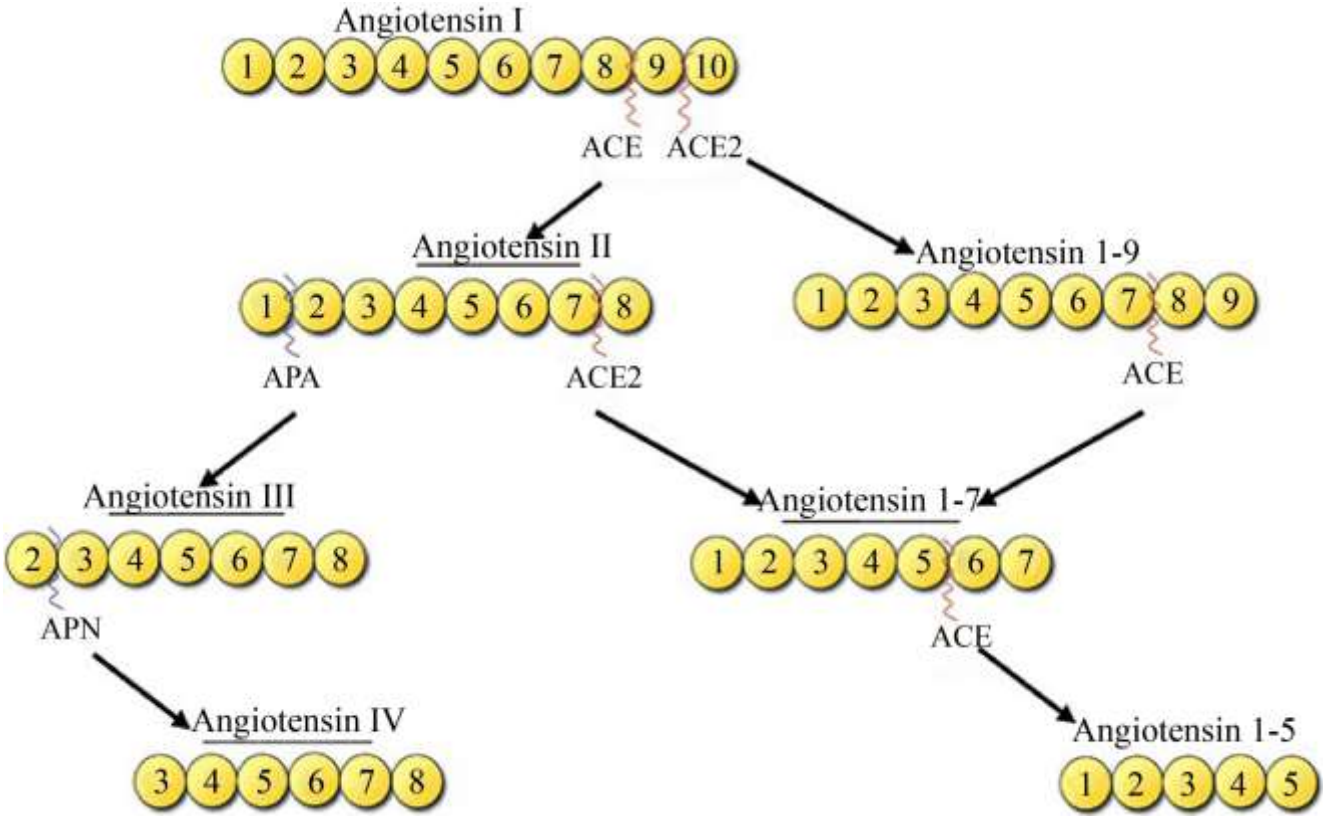

Fig. 1 The mechanism of formation of angiotensins by successive divisions of angiotensin 1

The main effects of RAAS result from the action of angiotensin II, which is an octapeptide produced either intravascularly or from the enzymatic divide of angiotensin 1 within the circulation by ACE.

Angiotensin II exerts multiple effects on the RAAS system [5]

- It contributes to maintaining water and electrolyte balance and water and salt retention through several mechanisms, most of which occur through the kidneys. It also works to regulate the volume of extracellular fluid through central mechanisms that depend on stimulating the secretion of vasopressin and the sensation of thirst. It stimulates the nerve cells within the blood vessels to produce the hormone norepinephrine and causes severe constriction of the smooth muscle cells of the blood vessels, which results in higher BP.

- It causes narrowing and remodeling of blood vessels by stimulating the rapid increase in numbers, relocation, and growth of smooth muscle cells of blood vessels, Which results in endothelial dysfunction and it causes a decrease in nitric, leading to an increase in blood pressure and associated cardiovascular and renal diseases, which include: Left Ventricular Hypertrophy (LVH), post-infarction remodeling, in addition to stiffness Renal vessels.
- Angiotensin II acts as an inflammatory mediator accused of causing atherosclerosis, as it stimulates the infiltration of white blood cells and the migration of smooth muscle cells in the vessels, Increased oxidation of LDL, in addition to the production of many harmful oxidants and reactive oxygen species that cause structural change and damage to the walls of blood vessels.
- Angiotensin II enhances the coagulation and oxidative stress state because it causes an increase in tissue factor, increases the activity of NADPH, and stimulates platelet aggregation because it contains receptors for it. It also induces the production of other factors, such as plasminogen activator inhibitor-1 (PAI-1). [8]

2.5. Angiotensin receptors (ATR)

2.5.1. Angiotensin II Type I Receptor (AT1R)

Angiotensin II exerts many negative effects on the heart, kidneys, and blood vessels, as its association with them causes a state of oxidative stress and causes a defect in the function of the blood vessels, as the vessels constrict severely.

The proliferation and migration of vascular smooth muscle cells occurs, causing thickening of the vessel walls and an increase in their resistance. Changes similar to the heart occur, and the activity of fibroblasts increases, leading to the re-formation of cells, the occurrence of programmed cell death, hypertrophy of the heart muscle, and an increase in the force of its contraction, thus increasing blood pressure. Activation of AT1R by angiotensin II also leads to activation of the sympathetic nervous system and increased production of aldosterone from the adrenal cortex, in addition to sodium retention and reabsorption by the kidneys. [5]

2.5.2. Angiotensin II Type 2 Receptor (AT2R)

Angiotensin II, through its binding to AT2R, has many positive protective effects. It exerts an anti-inflammatory role and limits the proliferation and migration of smooth muscle cells, thus preventing the remodeling of the heart and blood vessels. It increases nitric oxide levels, causing vasodilation. It also increases diuresis and prevents sodium absorption through the kidneys. Together, these effects contribute to lowering blood pressure. [5]

2.5.3. Mas-Receptor

This receptor binds angiotensin (1-7), leading to dilation of blood vessels, sodium secretion, combating vascular revascularization, and protection of the heart at physiological concentrations. [5]

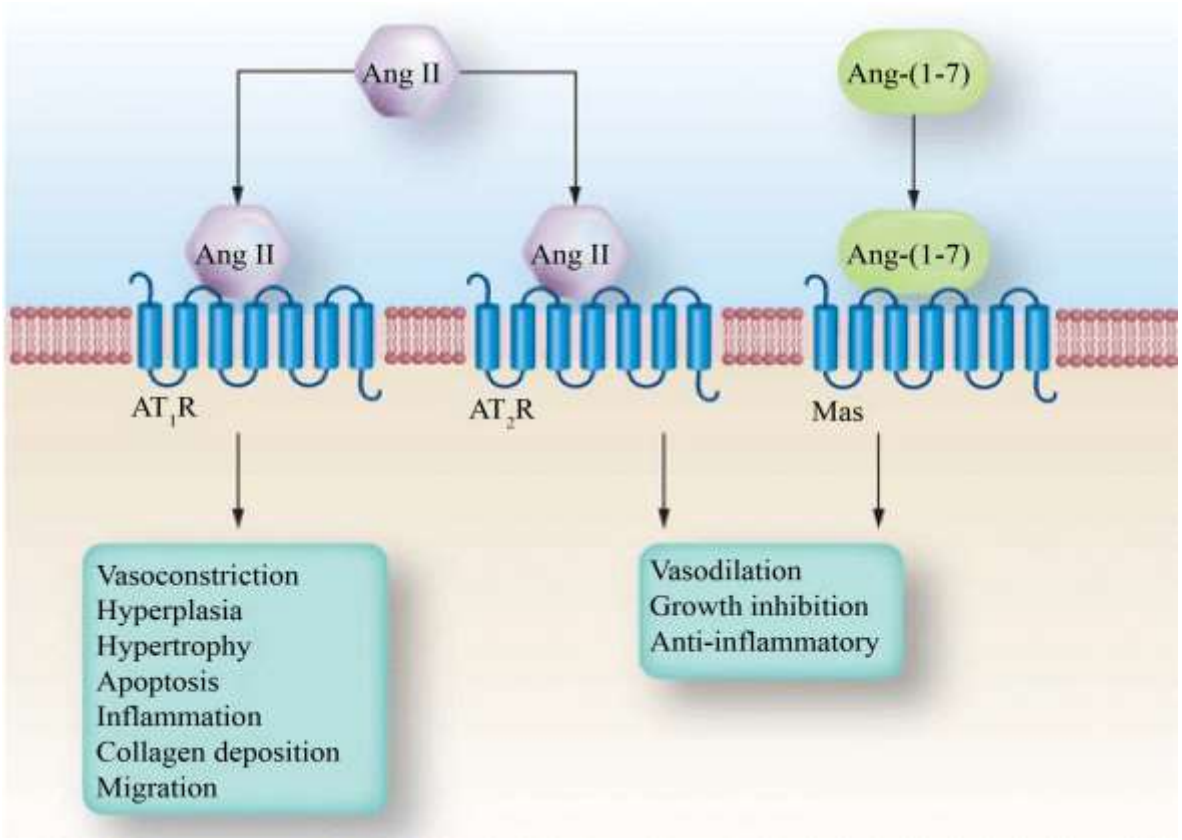

Fig. 2 Physiological effects resulting from the activation of different types of angiotensin receptors

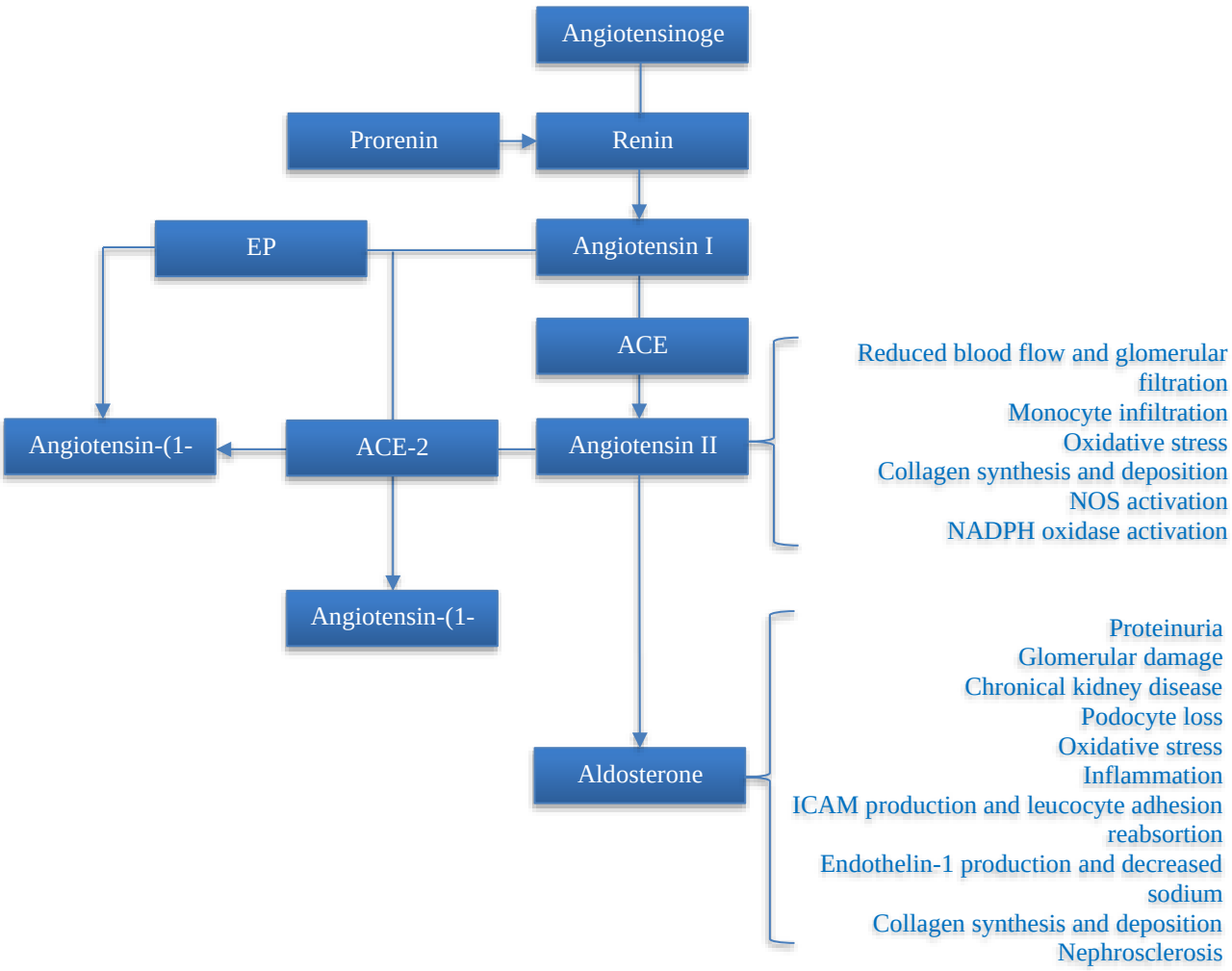

Fig. 3 Steps to activate the RAAS pathway and its pathogenic consequences

2.6. Aldosterone

Angiotensin II stimulates aldosterone secretion from the adrenal gland by acting on AT1R receptors. Aldosterone exerts its effects mainly at the kidney level by controlling potassium and hydrogen levels (it works to increase their excretion through the kidneys) as well as increasing sodium levels in the blood (by stimulating its reabsorption); it also increases blood vessel constriction through the effect of catecholamines, thus causing high blood pressure. hyper plasma aldosterone levels lead to increased of collagen 1 synthesis and proliferation of myocardial fibroblasts, leading to the replacement of contractile myocardial tissue with ineffective fibrous tissue and the occurrence of myocardial hypertrophy and failure of its function. This compound also exerts several external pathogenic effects that contribute to peripheral organ damage. [4, 5]

The sequential divisions that lead to activation of the RAAS pathway and the pathological effects resulting from angiotensin 2 and aldosterone are illustrated in Figure 3.

3. Primary Hypertension

High blood pressure is classified according to the causative factors into two types: idiopathic primary hypertension, also called Essential Hypertension (EH), which constitutes the vast majority of cases (90-95%), and secondary hypertension, which often results from the presence of a disorder In the endocrine glands of the body, its cause is usually known and is easily diagnosed through laboratory tests and examinations., and its percentage is approximately 5-10% of high blood pressure cases. [4, 9]

Primary hypertension is a widespread, complicated medical condition and is considered a global health problem. It affects 25-35% of adults and 60-70% of the elderly over 70 years of age and results from a complex interaction between genetic and non-modifiable epiginitic factors. The most important of which are:

- Genetic background: The genetic cause constitutes 25-60% of cases, and analyses conducted at the level of the complete genome showed the presence of 118 genetic sites associated with blood pressure, as well as many genetic polymorphisms that may affect the synthesis of proteins and cause the development of the disease.
- Sex: High blood pressure is more common in men than in women of reproductive age. This is due to the protective effects of the estrogen hormone, as it contributes to protecting the heart and blood vessels. In

contrast, the incidence of high blood pressure increases in menopausal women due to low estrogen levels, as women and men have similar blood pressure values at ages over sixty (after menopause). At older ages (over 70 and 80 years), blood pressure values in women are higher than in men.

- Aging progress: Blood pressure tends to rise with age. At the ages of 35 to 40 years, systolic blood pressure is observed to rise due to metabolic processes or as a result of genetic causes. Systolic blood pressure increases in the elderly. Due to atherosclerosis, a decrease in kidney function and a lack of physical activity, while diastolic blood pressure decreases with age throughout an individual's life. [10]
- Ethnicity: Racial differences greatly influence the prevalence of hypertension among individuals within the same community.[11]

In the United States, the prevalence of HTN among Indians of American descent was similar or slightly higher compared to the general population, while Indians of Spanish origin were less susceptible. To contract the disease the prevalence rates were highest among African Americans. The rate was similar or slightly higher compared to the general population, while Indians and Hispanics were less susceptible to the disease, and prevalence rates were highest among African Americans.[4]

- Environmental factors: Air pollution, noise exposure, and ambient temperature have recently been considered among the environmental factors that predispose to chronic hypertension. [9, 12]
- Lifestyle factors: The fat, salt, and mineral content of the diet greatly affects blood pressure, as low calcium intake, excess saturated fat and salt, and low potassium intake lead to high BP. Increased plasma levels of sodium lead to water retention, resulting in an increase in blood volume and hypertension. Low calcium intake leads to stimulation of the parathyroids, increased absorption of calcium from the intestine, and decreased calcium excretion through the kidneys, thus increasing the concentration of calcium inside cells, which stimulates vascular smooth muscle and increases vascular resistance.

Cigarette smoking predisposes to coronary heart disease because nicotine causes constriction of the vessels and accelerates the heartbeat, which leads to a temporary increase in blood pressure. Excessive alcohol consumption also increases high blood pressure by a rate of 1.5 to 2 times, as its presence in the bloodstream increases blood vessel tension and thus causes high pressure.[12]

A sedentary lifestyle that leads to obesity and weight gain also poses a high risk of developing hypertension, and this results from increased insulin secretion and many modifications that occur in the body, such as increased blood vessel thickness, arteriosclerosis, and increased heart rate due to increased adrenaline secretion, which increases pressure. Severe obesity has been considered one of the greatest risks for developing high blood pressure. Other risk factors include lack of exercise, psychological distress, and lack of hours of sleep. [12]

- Salt sensitivity: Salt sensitivity is evaluated by giving the individual an amount of salt of no less than 5 grams and monitoring blood pressure during the following hours. It is observed in salt-sensitive individuals that systolic blood pressure increases significantly by an amount of no less than 10 mm Hg, as salt intake in these patients causes an imbalance In the function of the vascular endothelium, it causes fibrosis, oxidative stress, and decreased nitric oxide production, It also has an effect on the gut microbiota, by reducing intestinal survival and activation of Lactobacillus spp. Salt-sensitive individuals experience increased immune system activity and T-helper activation, which increases blood pressure levels. [4, 9, 13]

The previous factors combine together to lead to primary hypertension by causing a defect in the cardiovascular system and increasing systemic vascular resistance, which is considered the first and main cause responsible for the disease, by influencing many of the main biochemical and physiological pathways regulating blood pressure, such as Sympathetic Nervous System (SNS), metabolic pathways, RAAS, immune inflammation, systems that control vascular function such as (endothelin system, nitric oxide, prostacyclin, natriuretic peptides, and other factors such as (reactive oxygen species, adiponectin, adrenomedullin), intestinal microbes, salt sensitivity.[4, 9]

The genetic background and changes within the genome of individuals greatly affect the mechanism of hypertension and the development of its complications. Therefore, recent research has focused on the role of genetic factors in causing hypertension, with the aim of arriving at a more convenient treatment.[1]

4. Genetics of Primary Hypertension

The genetic part plays a significant role in the pathogenesis of blood pressure, as it affects more than 25-60% of cases; the heritability of systolic blood pressure is evaluated to 15-40%, While the ratio of diastolic is within limits of 15-30%, The chance of developing HTN gets bigger if there is a family history of the condition in one or both parents, according to family studies, and monozygotic twins show a considerable relationship with the blood pressure phenotype than dizygotic twins.

Growing clues suggest that primary hypertension is not a monogenic disease but rather a complex syndrome with divergent genesis and development. It falls within the so-called "genetic imbalance syndromes" that are caused by genetic components such as polygenic variants in addition to the influence of Epigenetic elements and interactivity between genes. Interlinkage observed between genes and the gene environment, where the incompatibility of genotypes with environmental surroundings leads to the

development of an adaptive genotype in the patient and the appearance of different blood pressure phenotypes specific to each patient individually. [1, 4]

In the case of primary HTN, the affected individuals have a common feature, which is high blood pressure, while they vary in genetic and environmental factors (the familial connection is 60%, and the environmental connection is 40%). [14]

According to the genetic footing, HTN may be monogenic, which is the outcome of mutations in one gene, leading to the early appearance and severe blood pressure phenotype. Monogenic syndromes all have the same blood pressure phenotype, but they differ in clinical and laboratory features and causative genetic mutations; studying genetic mutations has contributed notably to understanding the genetic basis of the main pathways regulating blood pressure, such as sodium balance and the RAAS system. [14]

The other sort of hypertension is the multigene and multifactorial form, which is an expanded mosaic form from the previous scaled-up mosaic form, as it results from a secondary variance in the single causative genes and the presence of interlinkages between these genes that lead to the emergence of moderate types of HTN. For example, individuals of African descent tend to have a salt-sensitive form of HTN in contrast to Europeans, and somatic mutations causing hyperaldosteronism lead to another subset of HTN. [14] perception of the variety and intricacy of the causes of high blood pressure, which Page explained within the mosaic theory, is likely to open new horizons for the stratification of hypertensive patients and the development of individual drugs according to precision medicine. [3]

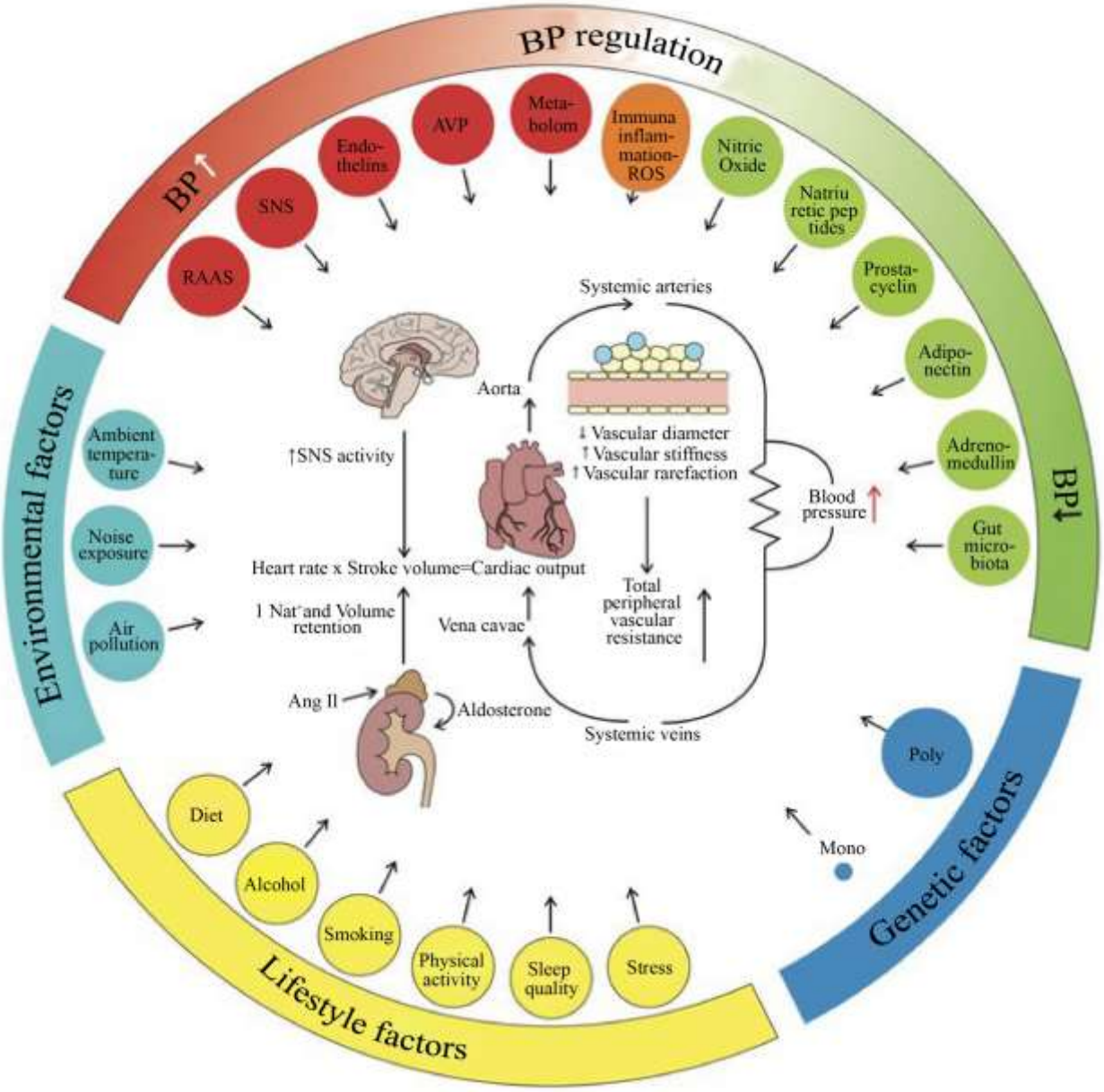

Fig. 4 The complex interactive mechanisms causing the initial pressure rise

Disturbances of the RAAS play an essential effect in the pathological mechanism of hypertension and also in causing its accompanying complications. 30 to 50% of the variation in the occurrence of EH is due to an inherited cause, as more than 150 genes contribute to the emergence of the final form of this complex disorder.[7] Attention was paid to the genes encoding components of the RAAS. This is because many antihypertensive agents widely used in the therapeutic management of hypertension aim to inhibit the RAAS pathway by targeting its various components. These genes encode components of the RAAS and include: [5]

4.1. The Renin Gene (REN)

The renin gene extends a distance of approximately 11.7 kb within chromosome 1, and it contains nine introns, while the number of exons is ten in this gene. Both the renin and pepsinogen genes belong to a common ancestral gene.

4.2. Renin Binding Protein (RENBP) Gene

The RENBP gene consists of eleven exons and ten introns. It extends approximately ten kilobases and is located on the long arm of the human X chromosome.

4.3. Angiotensinogen Gene (AGT)

The AGT gene is placed on chromosome 1, on its long arm and in the band 42.2. It occupies more than 12,063 base pairs (bp) and consists of five exons separated by four introns.

4.4. Angiotensin-Converting Enzyme (ACE) Gene

This gene is also called human Human-ACE or ACE1. Its genomic location is within chromosome number 17, where it occupies a region of its long arm (17q23). The number of exons within it is 26, while introns constitute a smaller number consisting of 25. This gene occupies a space within the genomic DNA that is estimated at 21 kb.

4.5. Angiotensin-Converting Enzyme 2 (ACE2) Gene

The ACE2 gene encodes a protein very similar to ACE1, and it is located on the X chromosome at the band 22.2 of the short arm of the chromosome.

This enzyme, which belongs to the dipeptidyl carboxydipeptidase family, is secreted by many organs to contribute mainly to protecting the heart as well as blood vessels. It converts angiotensin II into a protective compound with a vasodilating effect called angiotensin 1-7. This encoded enzyme is considered a receptor for the spike protein. of human coronavirus.

4.6. Angiotensin 1 Receptor Gene (AGTR1)

This gene takes place within chromosome 3 (3q21 – q25) [36, 37]. It contains a number of exons of at least five, which may reach a size of 2014 base pairs. This gene occupies a space within human DNA equivalent to more than 55 kilobases, and the number of amino acids within the protein encoded by this gene is approximately 359 amino acids.

4.7. Aldosterone Synthesis Gene (CYP11B2)

This gene, which contains nine exons separated from each other by eight introns, is located on band No. 24.3 within the long arm of chromosome No. 8. Figure 5 shows the genes involved in RAAS.

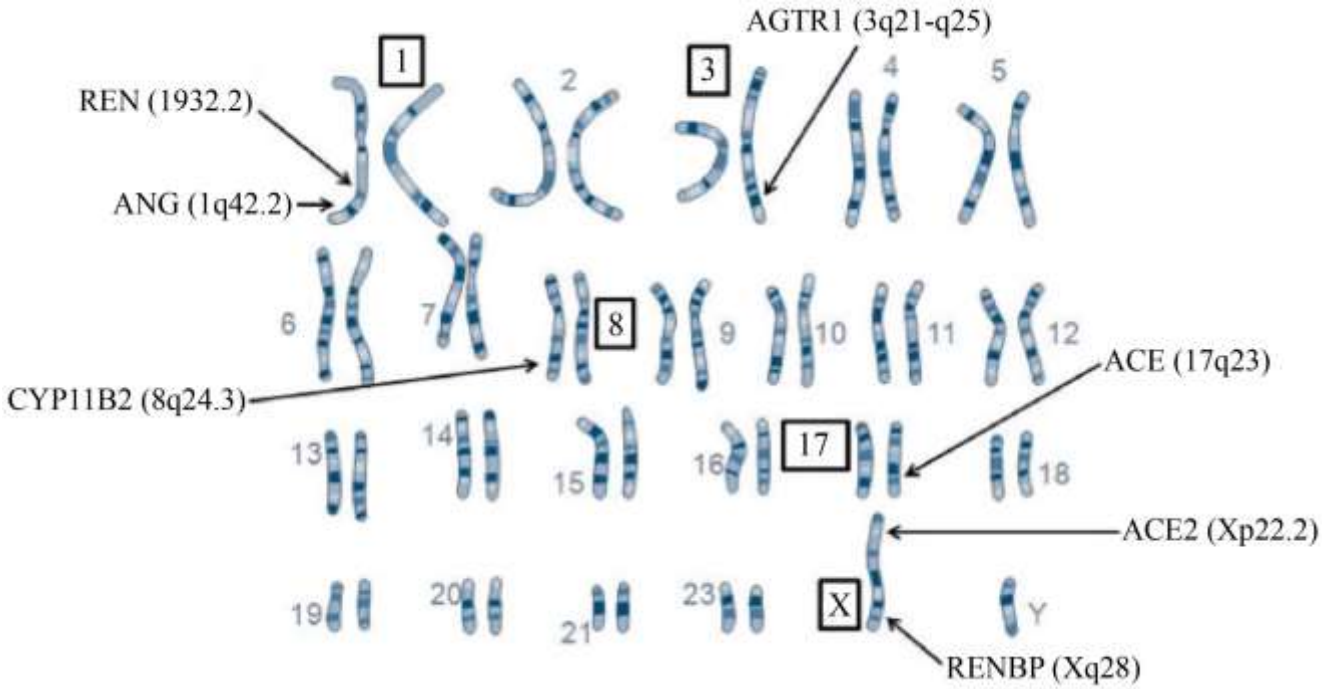

Fig. 5 Schematic showing the genes that encode the components of RAAS and where they are situated inside their chromosomes The numbers of the chromosomes in which the RAAS genes are located are boxed. Abbreviations assigned to gene names are followed by the location of the genes within the chromosome. The short arm of the chromosome is denoted by the symbol P, and the long arm is denoted by the symbol q.

5. RAAS Polymorphisms

Many abnormalities may occur in RAAS genes, the most dominant of which are Single-Nucleotide Polymorphisms (SNPs), which result from the substitution of a mutant nucleotide in place of a normal nucleotide due to transcription errors. SNPs may happen in a natural manner, but they may also be inherited from parents to children, leading to pathological appearance that may begin in fetal life.[5]

The polymorphisms may be of the synonymous type that does not modify the form of the protein or the amino acid arrangement. This type composes the larger part of SNPs, which amount to 162 million, as stated by Kaviar data, which included investigated variants. The other sort of single polymorphism is the non-synonymous that acts on the degree of gene expression by making a difference in the structure of protein and the arrangement of nucleic acids within it. [15, 16]

Since 2017, numerous studies have estimated the role of RAAS polymorphisms in the context of precision medicine, as these genetic variants have been linked not only with cardiovascular disease but also with many other endocrine and psychiatric disorders, intoxication with certain heavy metals, and levels of certain chemical compounds in the blood. [3] There are many factors that affect polymorphisms of genes, the most prominent of which is Ethnicity. Therefore, the relationship between the polymorphisms of RAAS genes and the incidence of primary hypertension and other diseases has been widely focused on across many studies that include different ethnicities. [15] Genetic modifications lead to disruption of the function of the RAAS system and result in variation in the disease phenotype between individuals. [1]

The following table shows the most important polymorphisms and pathological disorders correlated with them.

Table 1. Polymorphisms in RAAS genes and related diseases

Gene	Polymorphism	Investigated issue
REN	rs2368564	Preeclampsia, left ventricle diastolic dysfunction, in-stent restenosis
	rs5707	preeclampsia/eclampsia
RENBP	rs78377269	BP response to sodium intake
AGT	rs11568020	Pro-arterial hypertension, protection against arterial hypertension
	rs1190025960	Survival of gastric and breast cancer
	rs2478544	Elevated BP in women
	rs267598410	Survival of gastric and breast cancer
	rs4762	Pro-arterial hypertension, protection against arterial hypertension, diabetic nephropathy,) ischaemic heart disease, in-stent restenosis
	rs5050	Pro-arterial hypertension, protection against arterial hypertension
	rs699	Pro-arterial hypertension, protection against arterial hypertension, ischaemic heart disease, in-stent restenosis, diabetic nephropathy, end-stage renal disease, severity of symptoms in COVID-19
	rs7079	Blood lead level
ACE	rs1799752	Severity of symptoms in COVID-19
	rs4335	Risk of sudden cardiac death in hemodialyzed patients
	rs4340	Susceptibility to mycoplasmatic pneumonia in children
	rs4343	Risk of sudden cardiac death in hemodialyzed patients
	rs4353	Risk of sudden cardiac death in hemodialyzed patients
	rs9905945	Prognosis in sarcoidosis
ACE2	rs1514283	arterial hypertension in women
	rs2074192	Severity of symptoms in COVID-19, LV hypertrophy
	rs2106809	left ventricle hypertrophy
	rs4646155	arterial hypertension in women, left ventricle hypertrophy
	rs4646176	arterial hypertension in women, left ventricle hypertrophy
	rs6632677	Arterial fibrillation in men
	rs879922	arterial hypertension in women
AGTR1	rs12721297	Reduction of BP
	rs14922099	Arterial fibrillation
	rs5186	Diabetic nephropathy, breast cancer
CYP11B2	rs1799998	Acute coronary syndromes
	rs542092383	Risk of arterial hypertension
	rs73715282	Risk of arterial hypertension
	rs7463212	Risk of arterial hypertension

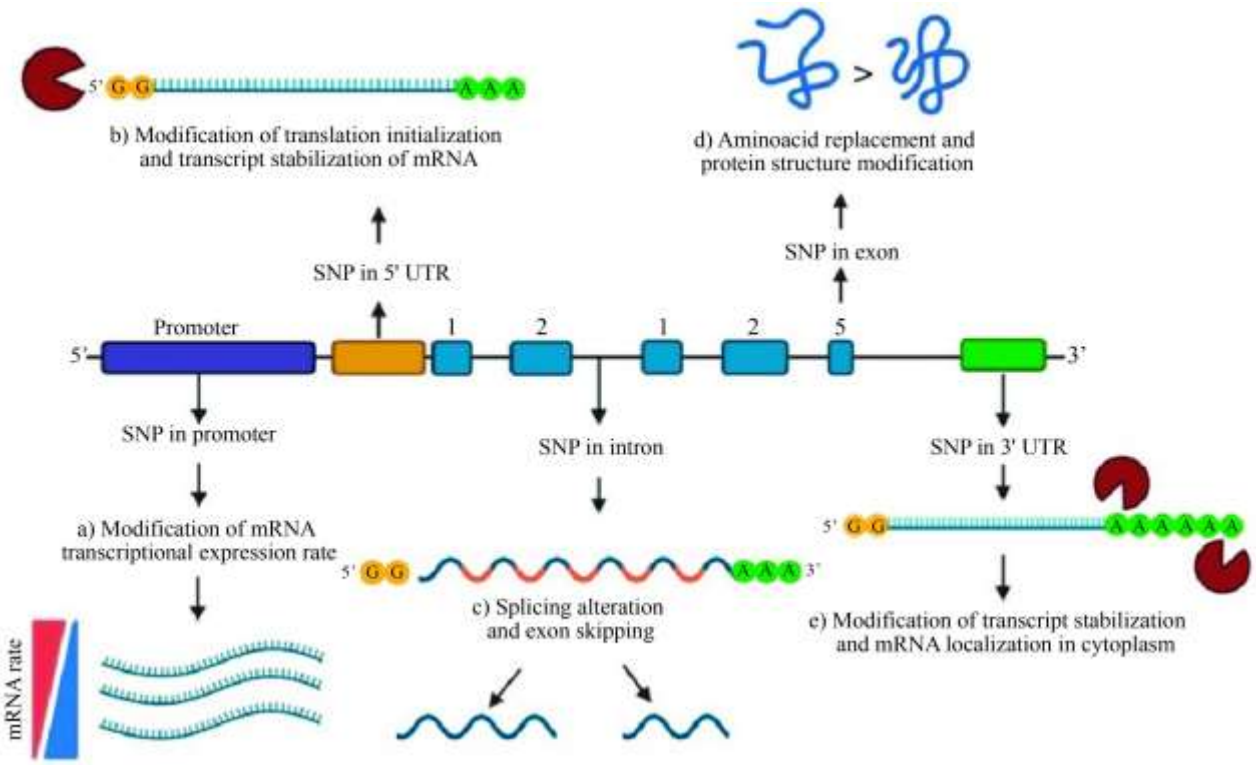

Fig. 6 Differential effects are linked with the site of occurrence of SNPs

6. Methods

In this review, several search engines were used, including: (Google Scholar, zlibrary, Pubmed), where the following keywords were used (renin-angiotensin-aldosterone system (RAAS), primary hypertension, SNPs, Candidate RAAS genes, polymorphisms) In order to access the information for this article, the most important polymorphisms associated with RAAS genes were searched, a systematic review of the presence of articles was carefully conducted, and a complementary reference list was linked to the articles studied was added in order to enrich the research and provide it with additional information.

7. Discussion

The genomics of hypertension is considered one of the major summonses in the field of research due to the great variation in the inheritance of the disease and the differences in treatment response and phenotypes in patients after successive discoveries in the genome-wide era, which aspired to search for common SNPs involved with EH, through GWAS studies that scan the complete genome to find attachment between genetic variants and blood pressure phenotype. [1]

Single-nucleotide polymorphisms may drive numerous effects that may be desirable, including a disease-preventive effect, or they may be hurtful to the body and predispose to the occurrence of disorders by causing a defect in the pathways regulating the various body systems. [17]

The molecular functional effects of SNPs vary depending on whether they are located in the coding or non-coding regions of the gene. Polymorphisms in promoter regions may repress gene expression by modifying the shape of the transcription factor binding site, or its effect is limited only to modifying the expression of this gene. The presence of SNPs in the 3′ untranslated (3′ -UTRs) also causes modification translation preparation and stabilizes the stability of the messenger RNA transcript, and SNPs in the intron regions work to bring about a change in the splicing process, modifying nuclear export, transcription rate and transcript stability. Non-synonymous polymorphism occurring in the exon region leads to an alteration in the sequence of the protein amino acids or the expression degree of the gene. SNPs in the 3′ untranslated UTRs may affect transcript stability and messenger RNA stability within the cytoplasm as Figure 6 shows.[18]

According to what was mentioned previously, the pathogenic mechanisms of RAAS SNPs genes convert greatly depending on the gene correlated with them and the location of their occurrence, and thus result in many different disorders; for example, In many studies, renin has been associated with preeclampsia in women, as well as the occurrence of eclampsia, Therefore, studying genetic variants of renin was extremely important in pregnant women.

More than 90 SNPs have been discovered that may occur within the renin gene, leading to the activation of the transcription factor SP-1, increased transcription rates of the renin gene, and increased plasma renin activity [19], which outcomes in increased formation of angiotensin II, which is characterized by varying effects that raise BP, by causing sturdy vasoconstriction, water and sodium retention, and reshaping the walls of blood vessels and thus increasing their resistance. [5]

The most important polymorphisms of this gene was rs236856, which was associated with preeclampsia, and this is due to the effects of RAAS on the formation of the placenta, as it leads to a defect in the lining of the spiral arteries and causes distortion in them through their remodeling, and this is what was studied by Lucia Maria and others.

Other studies also found an association between renin rs236856 polymorphism linked with left ventricular diastolic dysfunction and in-stent restenosis, rs5707 was also shown to be connected to eclampsia. [5]

Several polymorphisms in the AGT gene lead to increased gene expression in liver and heart cells, leading to increased levels of plasma AGT protein [20], which is the unique precursor of RAAS, and results in the formation of more angiotensin II, which works with AGT to promote myocardial hypertrophy through cell remodeling, fibroblast activity, and stimulation of myocyte proliferation and migration. Increasing the thickness of vessels and fibroblast proliferation, which results in hardening and resistance of the blood vessels, which in role leads to high BP, and the development of diabetic nephropathy as a result of disruption of its blood vessels. [5, 21]

The relationship between Genetic variants of AGT and their haplotypes with arterial hypertension has been investigated in several studies, the most prominent of which are rs5050 and rs11568020, which are placed within the promoter region of the gene, as well as rs699 and rs4762, which may occur within exons (in exon No. 2). [5, 22]

Khatami et al. found a Notable relationship between rs4762 and rs699 and ischemic disease of the heart, as well as with restenosis after More than 12 months of cardiac stenting was also associated with diabetic nephropathy, and Two polymorphisms were studied in patients with End-Stage Renal Disease (ESRD) on hemodialysis, where the rs699 genetic variant was associated with the presence of dialysis (ESRD), while the rs4762 polymorphism was not associated with the disease in these patients. [5]

The presence of the rs7079 polymorphism that occurs in the untranslated region of the gene is associated with the occurrence of hypertension associated with occupational exposure to lead. This is due to the fact that the genetic region in which the disorder occurs is necessary to bind microRNA that affects the transcription and translation of AGT, and thus rs7079 leads to increased serum concentrations of AGT and the development of hypertension with continued exposure to lead, the rs2468523 and rs2478544 polymorphisms were linked with higher values of systolic pressure in men, and this association is sex-dependent.[5, 6, 21]

The most common polymorphism affecting the ACE gene was an insertion or deletion (I/D) in the region of intron 16. The polymorphism in this region had a noticeable effect on serum enzyme concentration and activity, causing an increase in BP.

In recent years, many studies have focused on the association of polymorphisms (SNPs) of the ACE gene with inflammatory processes. The rs9905945 polymorphism has been associated in several studies with sarcoidosis. In children, the rs4340 polymorphism has also been associated with an increased risk and severity of pneumonia caused by Mycoplasma. The presence of genotypes (rs4335, rs4343, rs4353) had a role in protection against sudden cardiac death. In European-origin patients with chronic renal failure who are on hemodialysis, while a single genetic variant, rs4318, played a role in preventing SCD in these patients, as ethnic differences were observed.

A study conducted in China by Gaowa et al indicated a relationship between the ACE rs4295 genetic variant and cardiorespiratory fitness by affecting the level of peak oxygen uptake (VO2peak)), and the presence of the rs1799752 I/D (I/D ACE) genotype was linked with the seriousness of Covid-19 disease, the need for mechanical ventilation, and the following complications in patients, as well as with high baseline blood pressure in Asian and Caucasian populations.[1]

The ACE2 rs6632677 genetic variant has been associated with an increased risk of developing atrial fibrillation (AF) in men, hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM).

In women, five polymorphisms in ACE2 (rs2285666, rs879922, rs1514283, rs4646155, rs4646176) were strongly related to primary hypertension, and the genotypes (rs4646155, rs4646176, rs2106809, rs2074192) were associated with left ventricular wall hypertrophy left ventricular hypertrophy caused by height Arterial pressure. The two polymorphisms (rs2285666 and rs2106809) were associated with high baseline blood pressure.

The ACE2 enzyme contributes pivotally to the Pathogenic mechanism of COVID-19, as it binds to the spike glycoprotein of the pathogen, facilitating its passage into the host cell. The two studies, genetic polymorphisms rs2074192 and rs2285666, were associated with the seriousness of infection and increased likelihood of death in COVID-19 patients.

Many studies have been conducted about AGTR1 polymorphisms; in the study of Christodoulou, the AGTR1 rs5186 polymorphism was associated with retinal vein occlusion and ocular complications, and in another study, this variant correlated with a higher incidence of Nephropathy resulting from diabetes.

A significantly increased occurrence of breast cancer in women, The rs14922099 genetic variant, had a close relationship with the occurrence of atrial fibrillation (AF). It was associated with The presence of the rs12721297 polymorphism was correlated with low values in systolic pressure, while the 1166A/C polymorphism was associated with essential hypertension.

Genetic variation that occurs in the Aldosterone synthase (CYP11B2) gene greatly affects the bioavailability of aldosterone in the blood. The presence of the rs1799998 polymorphism in patients with chronic renal failure led to deterioration of kidney function and a a significant lack in glomerular filtration rate, and it has also been associated with acute coronary syndrome and cardiovascular and cerebrovascular events, Genetic CYP11B2 variants (rs542092383, rs73715282, and rs7463212) were also closely correlated with the risk of developing primary hypertension.

Polymorphisms of the RENBP gene have been related to hypertension, the most important of which was rs78377269, which was associated with salt sensitivity and dietary sodium intake in the study of Kelly et al. [5, 14]

The chief purpose of genetics studies such as this one, and the use of modernistic applied techniques such as Microarray, Sequenceflow-DNA, and NGS in the context of complex genetic diseases such as hypertension, is to secure further understanding of the main genetic mechanism causing the disease and to highlight the role of pharmacogenomic therapies. And pharmacogenomics in the treatment of HTN in the future, by reusing drugs according to the genotypes present in each patient patient that provide optimal blood pressure control. [3, 23]

The most important thing is to reach the final treatment for genetic diseases in the future through genetic modification using genome editing techniques that work to enzymatically cut out part of the gene, causing the mutation. [24]

9. Conclusion

This review highlights the crucial role of genetic etiology in the mechanism of occurrence of primary hypertension and the involvement of polymorphisms in RAAS genes in the pathogenesis and related complications like Coronary artery ischemia, hypertrophy, heart failure of the heart, renal disease in the end stages, ocular complications). The SNPs most closely related to essential hypertension were: (rs1799752 I/D) that related to ACE gene, (rs2285666, rs2106809) which observed in the ACE2 gene, 1166A/C in the AGTR1 gene, (rs542092383, rs73715282, rs7463212) in the CYP11B2 gene, in addition to (rs4762, rs699) in the AGT gene.

RAAS SNPs have also been associated with many other diseases such as (eclampsia, sarcoidosis, COVID-19 disease and the need for mechanical ventilation, atrial fibrillation, diabetic nephropathy, breast cancer, salt-sensitive hypertension associated with occupational exposure to lead, and left ventricular diastolic dysfunction. , acute coronary syndrome, cardiovascular and cerebrovascular accidents, and in-stent restenosis).

It is recommended to start by developing a genetic profile for hypertension in Syria by investigating the prevalence of polymorphisms linked with RAAS, considering that the treatment plan for hypertensive patients in this region relies mainly on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which may indicate the possibility of the spread of RAAS SNPs in Syrian society.

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