Clinical and Experimental Health Sciences

Recent Developments in Adrenergic Receptor Polymorphisms in Essential Hypertension

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Received: January 6, 2025 **Accepted:** January 21, 2025

ABSTRACT

Objective: This review's goal is to provide an overview of the most recent data about the genetic foundations of adrenergic receptor polymorphisms in connection with essential hypertension (EH). Since EH is idiopathic, research is centered on its genetic underpinnings and significant interindividual differences in response to various therapies. Polymorphisms as an important element affecting individual disease susceptibility processes, are therefore, area of research interest for especially for genes that modulate variety of metabolic processes

Methods: A comprehensive, systematic literature search was conducted using a number of databases, including PubMed, Google Scholar, and Web of Science (WOS). Recent research in the field that looked into the connections between blood pressure, heart disease, hypertension, and vascular problems was taken into account. Only studies with common polymorphisms, uniform criteria and statistics were included in order to assess consistent information and provide a broad perspective.

Results: There are a limited number of studies in the literature after 2010 related to the adrenergic system polymorphisms, blood pressure, and/or essential hypertension. Genome-wide studies and meta-analyses reveal that there are several variants whose roles were supported by independent studies. ADRA1 Arg347Cys (rs1048101), ADRA2 C-1291G variant (rs1800544), ADRB1 Arg38Gly, ADRB2 Arg46Gly and ADRB3 Trp64ARg (rs4994) can be counted as major polymorphisms with their role verified by multiple researches.

Conclusion: Despite being supported by numerous research, the association between adrenergic system polymorphisms and essential hypertension cannot be conclusively established due to the unpredictability of study patient numbers, side effects, and inconsistent findings. Larger and more controlled population-based studies are required to provide a clear picture of the disease's variability and treatment responses.

Keywords: Adrenergic receptors, blood pressure, essential hypertension

1. INTRODUCTION

Catecholamines, a class of molecules with an amine chain and a catechol ring, are important components of the sympathetic nervous system. These consist of dopamine, adrenaline, and noradrenaline, the latter two are also known as epinephrine and norepinephrine. This family of molecules regulates the body's neurological and metabolic activities and serves as essential targets for a variety of pharmaceutical medications.

Catecholamine polymorphisms have drawn attention since they play a significant role in the pharmacological effects of certain diseases. Sympathetic denervation directly relates to elevated blood pressure (BP) and heart rate, two characteristics of hypertension, one of the most common disorders in the world, especially in the elderly (1). Essential hypertension (EH) is idiopathic, and there are a number of risk factors to take into account. The primary causes involve genetic basis in personal family history, dietary regime, aging, and obesity.

Studies linking more than 50 genes to hypertension have been conducted, and the number is continuously increasing (2). Currently, however, little is known about the hereditary component of hypertension. The genetic foundation of EH includes gene-environment interactions, epigenetic variables, and the interplay of several genes, each of which has a minor impact. Three main groups of protein families have emerged as a result of genetic research: adrenergic receptors, the renin-angiotensin-aldosterone system, and sodium reabsorption-regulating channels.

Through a current analysis of clinical findings, this review will briefly address the role of adrenergic receptor polymorphisms in EH. We examined the significance of

https://doi.org/10.33808/clinexphealthsci.1614451

these SNPs in the generation and treatment responses of EH by comparing published results. The role of adrenalin and adrenergic receptors, directly or indirectly correlated with the regulation of blood pressure (BP) and heart rate, will be overviewed in this perspective based on the current knowledge of the polymorphisms of the relevant elements. It is believed that this compilation will help to integrate current accumulated knowledge in the field, provide a preliminary perspective for the design of future studies, and increase our understanding of the SNP-related genetic basis of adrenergic system components in this one of the most prevalent and complexly structured disorders.

2. ADRENERGIC RECEPTOR POLYMORPHISMS

One essential part of the autonomic nervous system is the adrenergic system. In addition to controlling cardiovascular, respiratory, and metabolic processes and regulating blood pressure through its effects on the central nervous system, it also contributes to the regulation of renal sodium through renin-aldesterone-angiotensin system (3, 4). It operates primarily through adrenergic receptors, which react to the hormon/neurotransmitters adrenaline and noradrenaline. The adrenergic system orchestrates wide range of physiological responses to stress and activity. Adrenaline is secreted mainly by the adrenal medulla and it enhances systemic effects like elevated heart rate, vasodilation, and energy mobilization during stressful situations. Noradrenaline is a neurotransmitter that is released by sympathetic nerve terminals, whereas adrenaline is mostly classified as a hormone. Two main classes of adrenergic receptors are distinguished by their pharmacological and functional characteristics: a-adrenergic receptors (α1 and α2); β-adrenergic receptors (β1, β2, β3). Additionally, each a group has also been subdivided into α1A, B and D; α2A, B and C (5). The receptor classes are schematically represented in Figure 1, together with the most extensively studied polymorphisms linked to hypertension and blood pressure. An overview of studies examining the relationship between AR polymorphisms and blood pressure or hypertension that were discussed in this review is presented in Table 1.

Table 1. *A summary of recent studies on adrenergic receptor polymorphisms in relation to blood pressure and hypertension.*

Reference (Ref. No)	SNP	Ethnicity	Sample size (HT/NT)	Association/ significance	Parameter
Adefurin et al. 2017 (10)	ADRA1B rs10070745	Caucasians and African Americans	105	Yes	Arterial pressure
Eldeeb et al. 2022 (18)	ADRA2B rs1800888 (301-303 I/D)	Saudi population	200 HT/100 NT	No	Hypertension with Type 2 diabetes mellitus
Wu et al. 2015 (25)	ADRB1 rs1801253 (Arg389Gly)	Chinese	93	No	Essential hypertension
Chen et al. 2018 (26)	ADRB1 rs1801253 (Arg389Gly)	Not specified	261/261	No	Essential hypertension
Varakantham et al. 2018 (30)	ADRB1 rs1801252 (Ser49Gly) rs1801253 (Arg389Gly)	South Indian	292/324	No	Essential hypertension
Cai et al. 2015 (35)	ADRB2 rs11168070 (-468 C/G)	Chinese Kazakh	150/150	No	Essential hypertension
Yan et al. 2020 (37) Meta-analysis	ADRB2 rs1042713 (Arg16Gly)	Chinese	3390/2528	Yes	Essential hypertension
Maamor et al. 2024 (39) Meta-analysis	ADRB2-rs1042713 rs1042714	East Asian	7269/7615	Yes	Hypertension
Li et al. 2018 (40) Meta-analysis	ADRB3 rs4994 (Trp64Arg)	Chinese Japanese German Italian	5088/4467	Yes	Essential hypertension

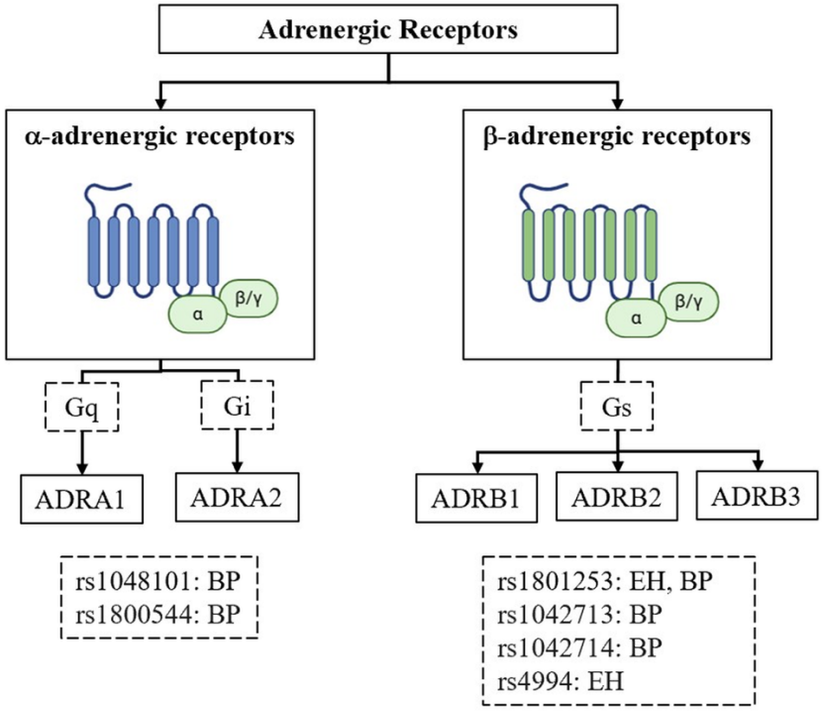

Figure 1. *The receptor classes, together with the most extensively studied polymorphisms linked to hypertension and blood pressure.*

2.1. α-adrenergic receptor polymorphisms

The α-adrenergic receptors are G-protein-coupled receptors, and they activate second messenger systems through the activation of G-proteins (G_q or $G_{i/o}$). α1 mediates vasoconstriction and is crucial for controlling vascular tone, whereas α2 controls the release of noradrenaline from presynaptic terminals (6).

α1-AR activation causes smooth muscle contraction in blood vessels (e.g., arteries, veins), leading to vasoconstriction. This increases vascular resistance, which raises blood pressure. The route proceeds via Gq-mediated activation of phospholipase C, which cleaves phosphoatidylinositol-4,5-bisphopshate (PIP2) to create diacylglycerol (DAG) and inositol trisphosphate (IP3). IP3 is a known messenger for Ca^{2+} release from intracellular stores. In addition to blood vessels, α_1-AR activation causes contraction of smooth muscles in other organs, such as the bladder, prostate, intestinal tract, and uterus.

The α2-ARs are found on pre – and post-synaptic neurons of the central and peripheral nervous systems and blood vessels. They play a significant role in regulating sympathetic tone through both central and peripheral sympathetic inhibition. They make substantial contributions to the homeostatic regulations, controlling contraction and relaxation of vascular smooth muscle, as well as other functions such as anxiety and stress-related behaviors, pain perception, platelet aggregation, and lipolysis.

The α2-ARs act through the G_i/G_o family of G-proteins in their physiologic functions, including vascular, cardiac, and metabolic systems, as well as the central and peripheral nervous systems. When agonists attach to receptors, the receptor couples with associated G-proteins, triggering effector reactions such as phospholipase C activation or adenylyl cyclase (AC) inhibition. However, their main role is G_i-mediated AC inhibition, modulating sympathetic activity to produce lower blood pressure and decreased heart rate.

The studies investigated the relation between adrenergic system polymorphisms and essential hypertension, blood pressure, and treatment response was compiled in our earlier work up to 2010 (7). Therefore, the interest of this review is limited only to the clinical articles published after this date.

In 2012, a genome-wide study found that among 28 pathways with biological relevance to hypertension, only ADRA1 pathway showed significant association with hypertension (8). However, this analysis included SNPs associated with genes implicated in the whole ADRA1 pathway, including those involved in the synthesis of norepinephrine and adrenaline, such as PNMT, MAO, COMT, GNAQ, GNA11 etc. Below is a summary of a small number of SNP research on α1-AR subtypes.

2.1.1. α1 (ADRA1)-adrenergic receptor polymorphisms

The human α1-AR is the predominant α1-AR subtype in vascular smooth muscle, the heart, and the liver. Considering its role in smooth muscle contraction, early research examined the connection between previously identified SNPs and hypertension. Compared to other adrenergic receptors, the relationship between ADRA1 and EH seems to be modest.

Given that α1A-ARs play a crucial role in controlling vascular resistance, multiple studies assessed the possible impact of the rs1048101 polymorphism with blood pressure readings both in healthy subjects or subjects with arterial lypertension. Three genotypes for the α-adrenergic receptors ADRA1A Arg347Cys (rs1048101, previously known as Arg492Cys), ADRA2A 1780 C>T (rs553668), and ADRA2B Del 301–303 (rs28365031) were investigated for exercise capacities, heart-rate recovery, and systolic and diastolic blood pressures in a healthy Brazilian population without any known cardiac issues. The maximum systolic blood pressure was found to be linked to rs1048101 in men and rs28365031 in women (9). Another variant was rs10070745 mutation, which contributed to the ethnic differences in phenylephrine sensitivity, a selective α1-AR agonist, and was significantly linked to vasoconstrictor responses to adrenergic stimulation (10). One study looked into whether α-AR polymorphisms affect how the body reacts to α-AR blockers. Based on the observation that interindividual variations remarkably affect blood pressure and side effects, a wide range of α1 – and α2 – variants were genotyped in 116 patients (11). The study examined a wide range of SNPs for α1A-variants, including variants of rs1048101 and rs2229125 linked to hypertension. Only two associations were discovered: the rs10515807 variant of α1B and the ADRA2A SNPs rs553668/ rs521674, which are both associated with higher dosages of α-adrenergic receptor blockers ($p < 0.05$) and a higher incidence of adverse effects ($p = 0.005$).

2.1.2. α2 (ADRA2)-adrenergic receptor polymorphisms

The function of α2-AR polymorphisms in BP regulation or essential hypertension has been the subject of numerous investigations. However, the majority of research examining the connection between hypertension and distinct polymorphic locations shows no correlation across ethnic groups. Although it has a clear role in controlling blood pressure, heart rate, and cardiovascular function, research examining the relationship between BP, EH, and genetic α2-AR variations yielded mixed findings (12-14). Kurnik et al (15) conducted a study in which they examined the cardiovascular responses of nine SNPs of ADRA2A (rs11195418, rs1800544, rs2484516, rs1800545, rs1800035, rs1800038, rs34303217, rs553668, and rs3750625) to the selective α2-AR agonist dexmedetomidine. Seventy-three healthy black and white American individuals, ages 18 to 45, participated in the study. A placebo group and a group receiving an infusion of dexmedetomidine participated in the trial. Out of all the variations, the rs553668 variant responded more strongly to the α2-AR agonist dexmedetomidine, whereas the others had no discernible impact. However, this study's small sample size led to some tiny genotype groups and broad confidence intervals; as the author noted, the results are preliminary and need to be confirmed in larger, clinical cohorts. Yağar et al (16), on the other hand, reported a promising association between (ADRA2A) C-1291G gene polymorphism (rs1800544) and response to dexmedetomidine.

Since Black Americans are known to have a higher risk of hypertension, a study looked at how their cardiovascular responses to stress may contribute to the development of hypertension. In normotensive individuals subjected to cold or psychological stress, the genotype analyses of ADRA1A Arg347Cys (rs1048101), ADRA2A C-1291G (rs1800544), and ADRA2B Insertion/Deletion (Ins/Del 301-303, rs1800888), showed that vascular reaction was more strongly associated with rs1800544, whereas heart rate reactivity was more closely linked to rs1048101 (17). A study carried out in Saudi population with 200 subjects, however, found no correlation between rs1800888 and hypertension (18).

Unfortunately, there are very few publications on this topic. It can be said that two polymorphisms associated with hypertension stand out in common from these studies:

α1A-AR polymorphisms Arg347Cys, especially linked to blood regulation, and a promoter variant of α2A-AR, C-1291G. The other SNPs in α1A, α1B, and α1D subtypes are the subject of ongoing research, and further studies are required to properly evaluate their contributions to hypertension.

2.2. β-adrenergic receptor polymorphisms

The β-adrenergic receptors (β-AR) couple to either G_s or G_i (heterotrimeric stimulatory and inhibitory G-proteins) proteins. Similar to α-AR, they are classified into three-subtypes: β1, β2 and β3. They act on the sympathetic control of heart rate and myocardial contraction. A mixed population of α-ARs are expressed in the human heart, with about 80% of the receptors being of the α1-AR subtype and 20% being of the β2-AR subtype (19). Any inhibitory effect on especially β1 receptor disrupting this approximate ratio whether in the gene regulation level, or in the protein level result in pathological heart problems (20). The receptor protein undergoes a conformational shift when β-AR agonist is present, which impacts the heterotrimeric G protein's ability to dissociate into its constituent subunits. A primary effect of the β-AR is stimulation of adenylyl cyclases, of which human cardiac tissues express several subtypes. Adenylyl cyclases catalyze the conversion of ATP to the second messenger cAMP, whereupon this interaction active catalytic PKA subunits are released. PKA alters a variety of cellular functions, from contractility to patterns of global gene expression, via phosphorylating serine and threonine residues on many proteins. Several important PKA targets are β-ARs themselves, L-type Ca^{2+} channels, the sarcoplasmic reticular Ca^{2+} /ATPase (SERCA) inhibitory protein (21).

β2-ARs induce bronchodilation and relaxation of smooth muscles. Defective β2-mediated vasodilation could result

in both increased arterial resistance and reduced venous compliance. β-ARs are useful targets for exogenously delivered inhibitory drugs, known as β-blockers. Mostly located in brown adipose tissue, the relatively new β3 receptor subtype contributes to the increase of lipolysis in this tissue and is also in charge of thermogenesis in skeletal muscles. There are many SNPs identified in the gene of β-ARs corresponding to different parts in structure (22).

2.2.1. ADRB1

The earliest studies on β1-adrenergic receptor polymorphisms dated back to 1999, where Mason et al (23) showed that replacement of Gly389 with Arginine resulted in a high affinity receptor-G_s complex, which in turn could result in pathological responses, especially in cardiovascular disorders. Similarly, Maqbool et al (24) reported two polymorphisms in a short communication (Ser40Gly and Arg389Gly), but they especially emphasized the substitution of the positively charged arginine for the neutral glycine for its effect in receptor / G protein coupling, thereby reducing efficiency of therapies based on β-AR antagonists.

Since then, numerous studies have examined the genetic variations of β-adrenoceptors and their connection to blood pressure and disorders of the cardiovascular system. Only work from the last 10 to 15 years was covered in order to provide an overview of the most recent advancements.

In a Chinese population study, Arg389Gly (1165 G>C) polymorphism was examined in 93 patients. Based on prior reports on the differential responses of patients with ADRB1 variant to β-blockers, the study analyzed reactions to metoprolol and shown that individuals with CC genotype had better outcomes than those with heterozygous GC mutations (25). A larger cohort with 261 EH patients treated with metoprolol through the same regimen were similarly investigated. Gly/Gly polymorphism in Arg389Gly ADRB1 was found to have a significantly improved metoprolol antihypertensive effect than those with heterozygous ADRB1, Arg389Gly (26).

An early meta-analysis of 5088 EH patients that included case-control trials prior to June 2012 revealed that the Gly allelic frequency of the Arg389Gly polymorphism was substantially lower in EH patients than in controls (27). Similarly, another meta analysis looked into systolic blood pressure, diastolic blood pressure, and hypertension in 29 136 people from 6 cohort studies in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. There was a significant linkage for rs1801253 in ADRB1 (Arg389Gly), with the Gly allele associated with a lower mean systolic blood pressure, diastolic blood pressure and prevalence of hypertension (28). In 2015, Ma et al. also collected and analysed reports on Arg389Gly for heart failure, involving 1736 participants. They were unable to demonstrate any link for this genotype, further confirming that larger cohorts, carefully selected sample population (family history, environmental characteristics, genetic etiology, etc.), and unbiased evaluations are necessary for conclusive interpretations (29).

An intriguing work compared protein mRNA expression levels rather than DNA sample variabilities to investigate the Arg389Gly (rs1801253) and Ser49Gly (rs1801252) polymorphisms in EH patients from the South Indian population. Contrary to earlier findings, this study found that Gly49Gly mRNA levels influenced antihypertensive medication responsiveness; however, they were unable to show any association with the risk of EH or a comparable effect on Arg389Gly (30). Although ADRB1 polymorphisms did not increase the genetic risk of EH, the increased Gly49Gly mRNA levels would indicate a possible contribution to the interindividual variations in drug response. According to a recent study including 147 individuals with hypertrophic cardiomyopathy, the Ser49Gly polymorphism can affect how well a patient responds to beta-blocker metoprolol, however the Arg389Gly polymorphism had no significant effect (31).

2.2.2. ADRB2

ADRB2 plays a potential role in blood pressure regulating by their action on vascular resistance, renin release, and renal sodium excretion (32). At 1998, Timmerman et al (33) reported four intragenic variants at the promoter region and N-terminus of the β2-AR in a study involving the offspring of 23 hypertensive and 22 normotensive European families. The position – 47 variant was substantially more common in children of hypertensive parents, and Arg46Gly at +46 was strongly linked to parental hypertension and elevated blood pressure in this sample pool. All variants were shown to be in linkage disequilibrium. The Arg16Gly and Gln27Glu alterations, which alter the extracellular portion of the receptor, were the main focus of later research; however, conflicting results also emerged as data collected from that time. A study with a large Northern Han Chinese population included 390 healthy participants and 747 hypertension individuals (34). Genotyping was performed to identify the C-47T, A46G and C79G polymorphisms of the ADRB2 gene. Compared to controls, hypertension participants had a substantially higher G allelic frequency of the A46G polymorphism. Linkage disequilibrium was detected between the C-47T, A46G and C79G polymorphisms. According to haplotype analysis, the T-47-A46-C79 haplotype protected against EH, but the T-47-G46-C79 haplotype raised the risk. A small study with a special cohort involving 150 individuals from Chinese Kazakh ethnic group has investigated 5'-UTR in six loci (35). Only the genotype and allele frequency distribution of the rs11168070 (-468C/G) locus showed a significant difference between the normotensive and EH groups. A46G (rs1042713, Arg16Gly) is one of the most studied genetic polymorphism found in ADRB2, and it has been demonstrated that the Arg16→Gly substitution amplifies the agonist-mediated receptor downregulation (36). A recent meta-analysis on the subject showed significant association with the risk of EH. This meta-analysis involved a total of 16 studies containing 3390 cases and 2528 controls (37). Another recent meta

analysis searched for the ADRB2 rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu). These polymorphisms were selected based on their documented impact on the augmentation of vascular resistance and their potential association with raised aldosterone levels, as essential hypertension is a salt-sensitive phenomenon (38). This meta-analysis displayed that ADRB2-rs1042713A allele carriers exhibited significantly lower basal blood flow and attenuated elevation in forearm blood flow as opposed to the G allele, similar to the results of Yan et al (39).

2.2.3. ADRB3

Mainly located in adipose tissue, β3 subtype is implicated in lipolysis, obesity, thermogenesis. The gallbladder, bladder, and brown adipose tissue all contain β3 receptors. Several studies have examined its connection to essential hypertension. One of the most recent papers was written by Li et al (40), who conducted a meta-analysis of 16 research with a total of 95555 patients to examine Trp64Arg polymorphism. Most of these studies focused on Chinese and Japanese ethnic backgrounds, with a smaller percentage of Caucasian people. Some of these studies found favorable connections, while others found none at all.

3. CONCLUSION

If predictors were appropriately categorized, blood pressure regulation may be improved and associated cardiovascular damage could be decreased. The genetic variants identified in the catecholamine pathways in connection with blood pressure regulation and hypertension have been the exclusive focus of this review. Because there aren't many studies released in the recent ten years, the selected works mostly featured meta-analyses on the issue of interest. Most of the studies in the field should be re-evaluated using larger and more controlled cohorts, and there are gaps that need to be filled. Ethnicity, sample power, sex, polygenetic variables or linkage effects, durations and consistencies of applied treatments, the reliability of control groups, etc. are some of the issues that always plague polymorphism investigations and lead to conflicting results.

Funding: *The author(s) received no financial support for the research.*

Conflicts of interest: *The authors declare that they have no conflict of interest.*

Ethics Committee Approval: *An ethics committee approval was not required for the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions:

Research idea: BE, İA, OO
Design of the study: BE, İA, OO
Acquisition of data for the study: BE, İA, OO
Analysis of data for the study: BE, İA, OO
Interpretation of data for the study: BE, İA, OO
Drafting the manuscript: BE, İA, OO
Revising it critically for important intellectual content: BE, İA, OO
Final approval of the version to be published: BE, İA, OO

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How to cite this article: Erdat B, Atlıhan İ, Orun O. Recent Developments in Adrenergic Receptor Polymorphisms in Essential Hypertension. Clin Exp Health Sci 2025; 15: 232-239. DOI: 10.33808/clinexphealthsci.1614451