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Association of AT1R (A1166C) gene polymorphisms and hypertension: A study in south Indian population and meta-analysis

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ABSTRACT

Introduction: Hypertension is a multi-factorial disease caused by several etiologies. It has been reported that hypertension has been linked to AT1R A1166C polymorphism, but the previous studies in Indian populations remain controversial.
Objectives: In this study, we aimed to investigate the AT1R A1166C gene polymorphism with the risk of hypertension in the south Indian populations.
Patients and Methods: The 179 subjects were considered in the association study utilizing polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) genotyping technique, yielding no significant association in the dominant and allelic models $P=0.76$ and $P=0.76$ respectively. Additionally, to determine the relationship between the AT1R gene A1166C polymorphism and hypertension in the Indian population, a meta-analysis was conducted. The retrieved seven case-control studies on Indian populations are conducted to determine how strongly genes are associated using the pooled odds ratio (OR) and 95% confidence intervals (CI).
Results: The meta-analysis was performed by RevMan software and significant association was observed in the dominant (AA versus AC+CC, $P=0.05$), recessive (CC versus AA+AC, $P=0.02$) and allelic (A versus C, $P=0.04$) models respectively.
Conclusion: The 'C' allele is statistically associated with an elevated hypertension risk in Indian populations.

Implication for health policy/practice/research/medical education:
The south Indian population case-control study reveals no relationship between the AT1R gene A1166C polymorphism and hypertension. However, the Indian meta-analysis study reveals the 'C' allele of A1166C polymorphism is statistically associated with elevated hypertension risk.
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Introduction

The renin-angiotensin-aldosterone system (RAAS) alteration was accountable for the development and progression of cardiovascular disease, progressive kidney disease, and essential hypertension, (1) . Among several genes studied in the RAAS, the angiotensin II type 1 receptor (AT1R) gene polymorphisms are biologically and clinically relevant to the pathogenesis and progression of renal disease and related to hypertension (2). Among several polymorphic sequence variants of the AGTR1 gene, the A1166C (rs5186), a trans version at 1166, is positioned in the 3′-Untranslated Region (3) and was the most well-studied in different populations. According to the reporter silencing assays, the 1166C allele lowers the miR-155 interaction with the cis-regulatory region and disrupts its base-pairing complementarity (4). Furthermore, a logarithm of the odds (LOD) score of 2.9 validates that the AGTR1 gene variants and hypertension

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are associated (5).

The data concerning the AT1R gene polymorphisms and hypertension found a significant association in Caucasians (6), and Asian populations (7). While the Nigerian (8), Kazakans (9), and Japanese (10) populations showed a lack of association. Furthermore, the study in South Indian Tamilian population (11) showed no association with essential hypertension. However, the other study conducted in North Indian Populations suggested that the AT1R A1166C gene C allele is linked with essential hypertension and its upregulation could play a vital role in it (12). In addition, early studies revealed inconsistent results with the correlation between the AT1R C 1166 allele and hypertension risk. Therefore, the study aimed to determine the AT1R gene polymorphisms, involved in the increased risk of developing hypertension in the South Indian population. Further, a meta-analysis was performed on data concerning Indian population to unravel the possible association between hypertension and A1166C polymorphisms of the AT1R gene.

Objectives

This case-control study is designed to investigate the AT1R A1166C gene polymorphism with the risk of hypertension and to perform the meta-analysis on the data concerning South Indian populations.

Patients and Methods

Study design

This case-control study consists of 179 subjects [70 hypertensive patients (61.4% of men) and 109 healthy volunteers as control (non-hypertensives) (60.6% of men)], recruited from Sri Ramachandra medical college and research institute, Chennai, Tamil Nādu, India. All subjects are from the geographical region of Tamil Nadu within south Indian origin. The demographic characteristics and clinical and biochemical variables were collected from all study subjects. The hypertensive subjects fulfilled the systolic blood pressure >140 mm Hg and a diastolic blood pressure >90 mm Hg. The 3 mL of blood sample was collected from all study participants.

Determination of genotypes

The phenol-chloroform extraction and ethanol precipitation method was used to isolate human genomic DNA from peripheral blood (13). The human AT1R A1166C variant sequence was detected with the specific primers: forward: GCACCATGTTTTGAGGTTG and reverse: CGACTACTGCTTAGCATA. The PCR process included an initial denaturation step in the thermocycler at 94°C for 10 min., followed by the PCR cycle which was repeated 35 times. This included denaturation at 94°C for 1 minute, annealing at 72°C for 1 minute and extension at 72°C for 10 minutes. The PCR products were digested with 10U DdeI restriction enzyme and then visualized on 2% agarose gels. For CC genotypes 417, 110, and 13 bp fragments were obtained and AA genotypes 527 and 13 bp PCR products were obtained.

Literature search strategy for meta-analysis

The computerized literature search was performed in various databases like PubMed, Google Scholar, and Scopus using key terms: "AT1R", "hypertension", "A1166C", "Indian population", "rs5186", "polymorphism" to retrieve the articles published exclusively in Indian population on AT1R A1166C polymorphism with hypertension till January 2023. Further, the retrieved articles were admitted to checking the eligibility with inclusion and exclusion criteria for the meta-analysis as mentioned in Figure 1.

Statistical analysis

The allelic and genotypic frequencies of AT1R A1166C polymorphism were evaluated using the gene-counting method. The χ^2 test with one degree of freedom was performed to test the Hardy-Weinberg equilibrium. Meanwhile, $P<0.05$ was considered significant. The association between the candidate gene polymorphism and hypertension was determined by the χ^2 association test. Statistical analysis was done using SPSS for Windows 10.1 (SPSS Inc., Chicago, IL), and for meta-analysis, the Cochrane Rev Man software version 5.4 (Cochrane library, UK) was used for testing heterogeneity and publication bias.

Results

Baseline clinical characteristics

Hundred and seventy-nine study subjects were included and genotyped in this present study. Of the genotyped individuals, the mean age of the subjects was 46.9 ± 10.4 years. The differences in age among the subjects were shown to have statistical significance ($P=0.001$). The studied characteristics of the groups were demonstrated in Table 1. Among the studied characteristics the creatinine ($P<0.001$), BUN ($P<0.001$), bicarbonate ($P=0.003$), potassium ($P=0.039$), and calcium ($P<0.001$) were found to have significant relation between hypertension and control groups. However, there were no significant differences between the other examined characteristics of sodium ($P=0.982$) and chloride ($P=0.900$; Table 1).

AT1R A1166C genotypes and hypertension

Among the subjects, 109 (60.9 %) individuals are non-hypertensive (male: 60.6%), and 70 (39.1%) individuals belong to hypertensive group (male: 61.4) and found no significant association ($P=0.906$). The genotype distribution between controls and hypertensive groups revealed that there was no significant association; AA versus AC, OR = 1.18, 95% CI = 0.39-3.56, and $P=0.764$. Furthermore, the allelic model revealed no significant association; A versus C, OR = 1.17, 95% CI=0.39-3.46, and $P=0.769$. However, it was found that there was a significant association in the family history of diabetes

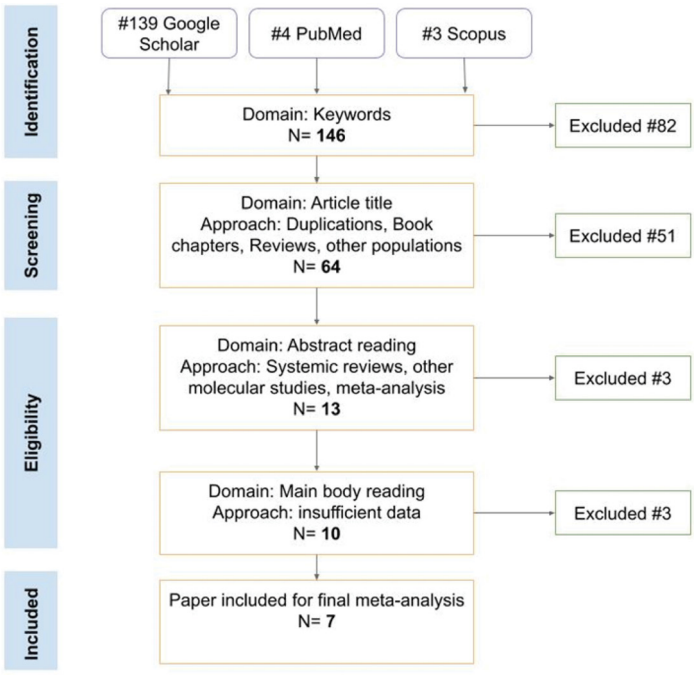

Figure 1. Schematic representation of the article selection process.

mellitus between the study groups ($P=0.001$; Table 2).

Study characteristics of meta-analysis

A total of 146 papers were retrieved from the mentioned databases published till January 2023. The review papers, meta-analyses, systematic reviews, book chapters, and molecular studies other than the Indian population were excluded from this analysis. Upon screening, seven case-control studies with 2750 individuals (hypertensives;1381 and non-hypertensives: 1369) from Indian populations fulfilled the criteria and were considered for the present meta-analysis. The retrieved information for the hypertensive cases and controls from the Indian population of their genotypes, allele frequencies, and Hardy-Weinberg equilibrium were documented in Table 3.

Meta-analysis

The analysis between hypertensive cases versus controls of AT1R A1166C polymorphism revealed substantial heterogeneity in the dominant ($I^2 = 69\%$) and recessive ($I^2 = 65\%$) models and high heterogeneity was noticed in allelic ($I^2 = 75\%$) model. The random-effect model (DerSimonian Liard) was adopted based on heterogeneity values, a significant association with hypertensive risk in dominant (AA versus AC+CC) (Q test, $P=0.002$, OR = 1.41, 95%: CI 1.01-1.98, overall effect: $P=0.05$) and recessive (CC versus AA+AC) (Q test, $P=0.02$, OR = 0.56, 95% CI: 0.34-0.92, and overall effect: $P=0.02$). Similar to the genotype meta-analysis, the pooled odds ratio for the allelic model (C versus A) showed a statistically significant association with hypertensive cases adopting random effect (Q test, $P=0.0002$, OR = 1.38, 95% CI: 1.02-1.85, overall effect: $P=0.04$) among Indian population (Figure 2).

Publication bias

In addition the publication bias of the literature was

Table 1. Clinical characteristics of study participants

Clinical characteristics	Controls (n=109) Mean ±SD	Hypertensive cases (n=70) Mean ±SD	*P* value*
Age (y)	52.6 ± 12.7	46.9 ± 10.4	<0.001
BUN (mg/dL)	13.5 ± 6.5	18.0 ± 9.0	<0.001
Creatinine (mg/dL)	1.1 ± 1.1	3.0 ± 2.6	<0.001
Sodium (mmol/L)	136.0 ± 6.6	135.8 ± 9.0	0.982
Potassium (mmol/L)	3.9 ± 0.6	4.4 ± 2.3	0.039
Chloride (mmol/L)	101.1 ± 6.1	100.9 ± 11.8	0.900
Bicarbonate (mmol/L)	24.5 ± 3.9	22.8 ± 4.4	<0.003
Calcium (mg/dL)	9.9 ± 1.7	7.7 ± 1.2	<0.001

BUN, bun urea nitrogen. * *t* test.

Table 2. Allele frequencies and genotype distribution of AT1R gene polymorphism in hypertensive and control

Genotypes		Control (n=109) (%)	Hypertensive (n=70) (%)	OR (95 % CI)	*P* value
AA		101 (92.6)	64 (91.4)	Reference	
AC		8 (7.3)	6 (8.57)	1.18 (0.39 – 3.56)	0.764
CC		0 (0)	0 (0)	-	-
A		210 (96.3)	134 (95.7)	Reference	
C		8 (3.6)	6 (4.3)	1.17 (0.39 – 3.46)	0.769
Gender	Male	66 (60.6)	43 (61.4)	Reference	
	Female	43 (39.4)	27 (38.6)	0.96 (0.52 – 1.78)	0.906
FH-DM	No	103 (94.5)	43 (61.4)	Reference	
	Yes	6 (5.5)	27 (38.6)	10.77 (4.15 – 27.9)	0.001

FH-DM, family history of diabetes mellitus; OR, odds ratio; CI, confidence interval.

analyzed in this study using Begg's funnel plot. The standard error and the odds ratio from the genetic models were conducted to generate the funnel plot. Figure 3 depicts the test performed in the analyzed genetic models and the symmetrical funnel plots denoted no evidence of publication bias for AT1R A1166C polymorphism in Indian population studies (Figure 3).

Discussion

In this present study, the AT1R gene did not have a strong association with hypertension in the south Indian population. The performed meta-analysis of AT1R A1166C polymorphism in controls and hypertensive cases showed a significant association in Indian populations. Additionally, heterogeneity among the studies depicted that all the dominant, recessive, and allelic genetic models revealed substantial heterogeneity. The publication bias was not reported.

The studies conducted on AT1R gene polymorphisms in association with hypertension in Indian populations yielded inconsistent results. Studies conducted by Chandra et al, in northern Indian populations (12), Parchwani et al on Gujarati subjects (14), and Patnaik et al from Odisha (15) explained the significance of polymorphism of the AT1R gene with the elevated hypertension risk. However, in contradiction to this, studies from Chandigarh by Chaudhary and Chaudhary (16), Ramu et al (11) on the south Indian population, Ashavaid et al on Mumbai individuals (17), and south Indian populations (18) failed to substantiate the association between the AT1R gene polymorphism and hypertension. Moreover, global studies found inconsistent results. Studies on Egyptian

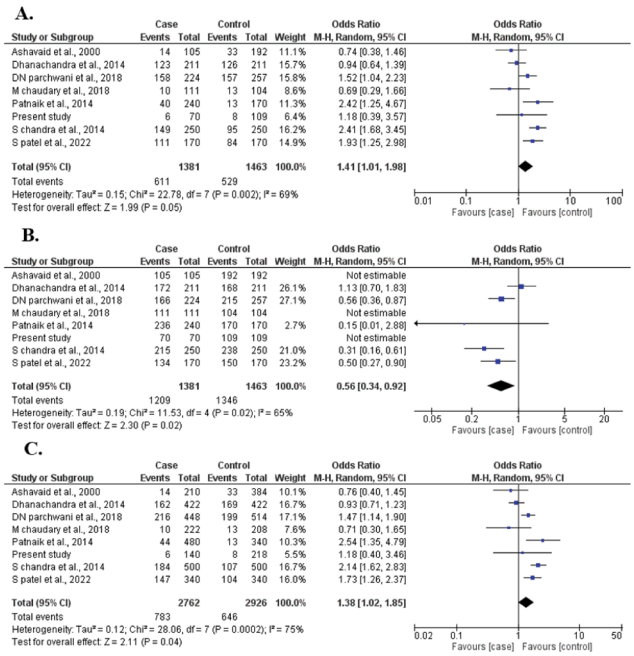

Figure 2. Forest plot showing individual and pooled ORs (95% CI) of the risk for AT1R A1166C polymorphism with hypertension and controls. **A.** Dominant model (AA versus AC+CC). **B.** Recessive model (CC versus AC+AA). **C.** Allelic model (C versus A).

Table 3. The distribution of AT1R A1166C genotypes and alleles for cases and controls among Indian populations

Author (Reference)	Genotyping method	Genotypes						Allele frequency				HWE	*P*[a]
		Case			Control			Case		Control			
		AA	AC	CC	AA	AC	CC	A	C	A	C		
Ashavaid et al (17)	PCR-RFLP	91 (87)	14 (13)	0	159 (83)	33 (17)	0	196 (93)	14 (7)	351 (91)	33 (9)	0.1927	1.69
Chandra et al (12)	PCR-RFLP	101 (40)	114 (46)	35 (14)	155 (62)	83 (33)	12 (5)	316 (63)	184 (37)	393 (79)	107 (21)	0.8359	0.04
Parchwani et al (14)	PCR-RFLP	66 (29)	100 (45)	58 (26)	100 (39)	115 (45)	42 (16)	232 (52)	216 (48)	315 (61)	199 (39)	0.3606	0.83
Patnaik et al (15)	PCR-RFLP	200 (83)	36 (15)	4 (2)	157 (92)	13 (8)	0	436 (91)	44 (9)	327 (96)	13 (4)	0.6042	0.26
Chaudhary and Chaudhary (16)	PCR-RFLP	101 (91)	10 (9)	0	91 (88)	13 (12)	0	212 (95)	10 (5)	195 (94)	13 (6)	0.4966	0.46
Patel et al (19)	PCR-RFLP	59 (35)	75 (44)	36 (21)	86 (50)	64 (38)	20 (12)	193 (57)	147 (43)	236 (70)	104 (30)	0.1392	2.18
Dhanachandra et al (18)	PCR-RFLP	88 (42)	84 (40)	39 (18)	85 (40)	83 (39)	43 (21)	260 (62)	162 (38)	253 (60)	169 (40)	0.0086	6.89
Present study	PCR-RFLP	64 (91)	6 (9)	0	14 (93)	1 (7)	0	134 (96)	6 (4)	29 (97)	1 (3)	0.8938	0.01

HWE, Hardy-Weinberg equilibrium.
[a] Chi-square test.

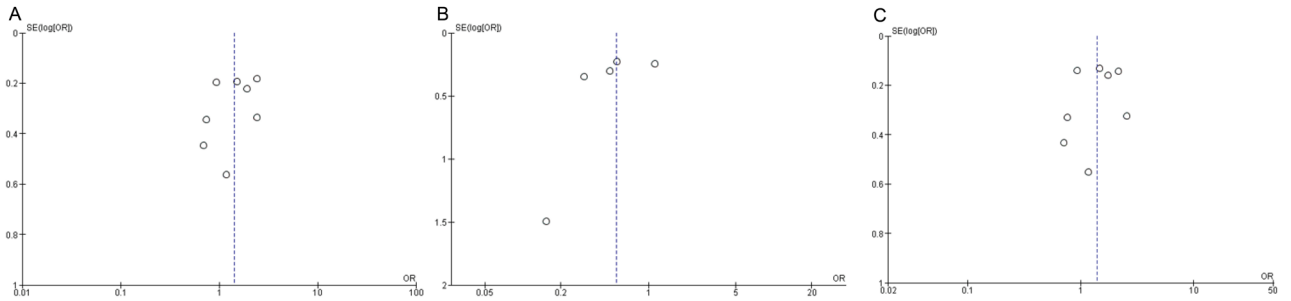

Figure 3. Funnel plots of publication biases on the relationship of AT1R A1166C polymorphism. Each point indicates the individual study included in the meta-analysis. (A. Dominant model, B. Recessive model, C. Allelic model).

populations (20), Calabar and Uyo (8), Sardinian (21), Jordanian (22), and Hispanic populations (23), showed no association between AT1R gene polymorphism and hypertension. On contrary, studies from Turkish (24), Polish (25), Lebanese (26), and Brazilian populations (27) revealed a significant interrelation between AT1R gene polymorphism and hypertension risks.

The support for the AT1R A1166C gene polymorphism in connection to hypertension has been strengthened by a meta-analysis study. A previous meta-analysis conducted by Liu et al, with 28 952 individuals from Asian and Caucasian populations found a significant association (28). Further, Wang et al, from Chinese population with 11 601 individuals revealed a significant association (29). Furthermore, the meta-analysis by Yang et al, with 22 857 individuals (30), Fajar et al, with 13 251 individuals (31), and Niu and Qi (32) with 16 474 individuals in an all-ethnicity populations found a significant difference between the AT1R A1166C with essential hypertension. Likewise, our meta-analysis observed a significant association between hypertension and AT1R gene polymorphism. In contradiction, Li et al, with 8493 individuals revealed that there was no significant correlation between the AT1R gene polymorphisms with pregnancy induced hypertension (33).

The mechanism underlying the relationship of essential hypertension with the AT1R A1166C polymorphism has been investigated since the 1166 A/C polymorphism is positioned in 3' UTR. Angiotensinogen produces angiotensin-I with the presence of renin, and the angiotensin-converting enzyme then catalyzes the synthesis of active angiotensin II. Ang II affects the morphology and function of major arteries by binding to AT1R and controlling inflammation, extracellular matrix deposition, and cell proliferation, these affect the density of AT1R though the polymorphism is present in the non-coding region (34). The AT1R A1166C polymorphism can reduce the ability of microRNA-155 to bind in the specific 3'UTR sequence, which can result in the onset of hypertension by the up-regulation of AT1R (35) . In spontaneously hypertensive rats and human aortic smooth muscle cells, oxidative stress was discovered to be a factor in the up-regulation of the vascular AT1R through the nuclear factor-κB (NF-κB) signaling pathway. Following restoring AT1R expression to baseline, pyrrolidine dicarbamate treatment, an NF-*k*B inhibitor, drastically slowed the hypertension progression in spontaneously hypertensive rats (36). In all central nervous tissues, including the spinal cord, and other functional areas of the brain in spontaneously hypertensive rats, the AT1R gene expression was favorably correlated with blood pressure (35). A recent study revealed that maternal exercise affected the offspring's mesenteric artery through the repression of the AGTR1 gene, by upregulating the expression of DNA methyltransferase in the spontaneously hypertensive rats and significantly reducing hypertension (37). Besides, it was noted in the study (38) that increased blood pressure is associated with high-fat diets, AT1R expression in the kidney and aorta were both upregulated in mice with the ingestion of high-fat high-sucrose diets, results yielded that utilization of berry lowered AT1R expression in kidney and aorta, resulting in reduced renal NADPH oxidases (NOX) and lessening the oxidative stress in endothelium reduces hypertension which is driven by the polyphenols present in the berries.

Conclusion

In conclusion, the study on AT1R A1166C polymorphism revealed no significant association in South Indian hypertensives. However, this meta-analysis illustrates that AT1R A1166C polymorphism significantly increases hypertension risk in dominant, recessive, and allelic models. The Indian population showed the presence of the C allele and the AC genotype is associated with a higher risk of hypertension. Further, studies could be extended to a larger number of hypertensive individuals to gain more evidence. Thus, offering an index of those who are 'at risk' and estimating the likelihood that they would develop hypertension in the future may be a powerful predictive classifier. The ability to classify hypertensive people according to their genetic makeup will assist in personalizing medication and expanding treatment options, and these studies can further support translational research.

Limitations of the study

Present research has some limitations. First, essential factors which regulate hypertension such as, body mass index, physical activity and other lifestyle characteristics were not considered to correlate with our findings. Second, the sample size included for this study was very small. Therefore, large number of samples with all essential factors are to be correlated to confirm our findings.

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Authors' contribution

Conceptualization: Sandhya Suresh and Gnanasambandan Ramanathan.
Investigation: AR, Sandhya Suresh, Ramprasad Elumalai.
Data curation: Harini Ravi and Gnanasambandan Ramanathan
Visualization: Gnanasambandan Ramanathan.
Writing–original draft: Amulya Ramakrishnegowda and Harini Ravi.
Writing–review and editing: Ramprasad Elumalai, Harini Ravi and Gnanasambandan Ramanathan.
Project administration: Sandhya Suresh and Gnanasambandan Ramanathan.

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Institutional Ethics Committee of Sri Ramachandra Medical College and Research Institute (SRIHER) approved the study protocols (IEC No: IEC-NI/09/MAR/08/09). After approval, upon written informed consent the 3 ml of blood sample was collected from all study participants. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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