

Prevalence of rs5186 (AGTR1 A1166C) and its association with risk factors in primary hypertension

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ABSTRACT

BACKGROUND The prevalence of rs5186 (AGTR1 A1166C) in the Mekong Delta remains largely unexplored. This study aimed to determine the prevalence of rs5186 in patients with primary hypertension at Xuyen A Vinh Long hospital and to investigate its association with some risk factors for hypertension.

METHODS A case-control study was conducted including 65 hypertensive and 65 non-hypertensive patients. Genotype analysis of rs5186 was performed using tetra-primer amplification refractory mutation system-polymerase chain reaction, and glucose level and lipid profiles were measured. Associations between single-nucleotide polymorphisms, biochemical indicators, and hypertension risk were evaluated using multivariate logistic regression. A dominant genetic model (AC + CC) versus AA was applied for rs5186, and false discovery rate correction was used to account for multiple testing.

RESULTS The genotypes of rs5186 in the hypertension group were 55.4% AA, 43.1% AC, and 1.5% CC, whereas in the control group, they were 64.6% AA, 35.4% AC, and 0% CC. The differences in the genotype distribution were not statistically significant ($p = 0.7$). The AC + CC genotypes showed no significant association with hypertension after adjustment for confounders. Among biochemical factors, elevated blood glucose (>6.5 mmol/l) was strongly associated with hypertension, with a 6-fold increased risk compared to individuals with normal glucose levels ($p < 0.001$).

CONCLUSIONS The rs5186 was not significantly associated with hypertension in this cohort, whereas metabolic factors, particularly hyperglycemia and obesity, were strongly associated with increased hypertension risk. Larger studies are needed to confirm the role of rs5186 and to examine the consistency of effect sizes across different populations.

KEYWORDS glucose, hypertension, PCR, SNPs, Vietnam

Hypertension is a prevalent global health condition with an increasing incidence worldwide, including in Vietnam. By 2025, the number of affected individuals could reach 1.5 billion.¹ The complications of hypertension, including stroke, cardiovascular diseases (CVDs), and renal failure, are among the leading causes of mortality.² According to the World Health Organization, the prevalence of hypertension increased from 27.7% in 2000 to

28.4% in 2015, highlighting its emergence as a global health burden.³ Recent studies emphasize that the increasing prevalence of hypertension is attributed to environmental factors and genetic variations.^{4–6} In Vietnam, hypertension has been on a concerning upward trend, prompting the Ministry of Health to integrate it into the national program for non-communicable disease prevention.⁷ The prevalence had increased to 28.7%, with 37.7% of patients on anti-

hypertensive medication but still failing to achieve optimal blood pressure (BP) control in 2017.⁸

Several studies have identified risk factors for hypertension, such as smoking, physical inactivity, age, sex, body mass index, blood glucose levels, lipid profiles, and the rs5186 polymorphism.^{5,6,9} Among these risk factors, genetic polymorphisms have attracted attention in the era of personalized medicine. Research on rs5186 has been conducted across multiple countries, demonstrating its association with hypertension and CVD risk.^{9,10} According to the Allele Frequency Aggregator database, the rs5186 polymorphism shows a high frequency of the reference allele A among Asian populations (91–92%), whereas the alternative allele C occurs at a lower frequency (8–11%).¹¹ East Asians display the highest A allele frequency (0.92) and the lowest C allele frequency (0.08).

The association between this polymorphism and hypertension has been studied; however, the findings remain inconsistent across populations.^{6,9,10} Semianiv et al¹⁰ reported that carriers of the C allele exhibited higher systolic and diastolic blood pressures (SBPs and DBPs) than AA homozygotes. In contrast, Shahin et al⁹ observed no significant overall association in a Middle Eastern cohort but observed that the polymorphism was linked to early onset hypertension in men with central obesity and a positive family history. Additionally, recent investigations have examined the role of this polymorphism in acute myocardial infarction-related mortality in southern Vietnam.^{12,13} The relationship between rs5186 and hypertension risk factors remains unclear. Therefore, this study aimed to determine the prevalence of rs5186 among patients with primary hypertension at Xuyen A Vinh Long Hospital and to investigate its association with the risk factors for hypertension.

METHODS

Study participants

This case-control study was conducted from April 2, 2023 to June 25, 2024 and included 130 patients recruited from Xuyen A General Hospital, Vinh Long Province, Vietnam. The study included 65 patients with (case group) and 65 without hypertension (control group), who were selected using a convenience sampling method with age and sex matching (aged 34–84 years). All participants were of Kinh ethnicity, the

predominant ethnic group in Vietnam. All participants provided written informed consent before being enrolled in the study.

The case group comprised patients diagnosed with hypertension based on the 2010 diagnostic and treatment guidelines of the Ministry of Health of Vietnam.⁷ The diagnostic criteria included an average SBP ≥ 140 mmHg and/or average DBP ≥ 90 mmHg, measured at least 2 times with a 1–2 min interval between the readings. If the difference between the two measurements exceeded 10 mmHg, additional readings were taken after a minimum 5-min rest, with the final recorded BP being the average of the last two measurements. Additionally, patients undergoing treatment for hypertension were included in the case group.

The control group consisted of individuals with SBP ≤ 120 mmHg and DBP ≤ 80 mmHg measured 2 times consecutively. Both groups provided informed consent to participate in the study and completed a questionnaire to collect baseline information and risk factors. The risk factors included smoking, defined as a history of smoking and categorized as “smoker” or “non-smoker”; physical activity, defined as engaging in brisk walking or moderate physical activity for at least 30 min, 5–7 days per week, and categorized as “physically active” or “physically inactive” according to the Vietnam National Heart Association (2022)⁸; and high salt intake, defined as consuming more than 5 g of salt per day (equivalent to one teaspoon) and categorized as “high salt intake” or “low salt intake.” Patients diagnosed with secondary hypertension were excluded from this study.

Biochemical analysis

Biochemical parameters, including blood glucose and lipid profiles, were assessed according to the diagnostic and treatment guidelines for hypertension provided by the Vietnam National Heart Association.⁸ The analyzed biochemical markers included glucose, cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), which were measured from heparin-anticoagulated plasma samples using an AU680 Clinical Chemistry Analyzer (Beckman Coulter, Germany). Reagents for glucose, cholesterol, TGs, HDL-C, and LDL-C were supplied by Beckman Coulter. Abnormal cutoff values for glucose >6.5 mmol/l, cholesterol >5.2 mmol/l, TGs >1.88 mmol/l, HDL-C <0.9

mmol/l, and LDL-C >3.4 mmol/l followed the guidelines of the Ministry of Health (2014).¹⁴

Genetic polymorphism testing

Genotyping of rs5186 was conducted using the tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) method, which involves several steps.¹³ First, 2 ml of venous blood was collected in EDTA-anticoagulated tubes, which were stored at 2–8 °C for up to 72 hours. Next, genomic DNA was isolated using a silica column-based method with the TopPURE® Blood DNA Extraction Kit (ABT, Vietnam) to isolate genomic DNA. For T-ARMS-PCR amplification, reactions were performed in a final volume of 20 µl, including 5 µl of the extracted DNA and 15 µl of the PCR mixture. The PCR mixture contained 4 µl of HOT FIREPol® MultiPlex Mix Ready To Load (ABT), 3 µl of 10 pmol primers (1 µl forward outer, 1 µl reverse outer, 0.5 µl forward inner, and 0.5 µl reverse inner), and 8 µl of distilled water.

The primers provided by Phusa Genomics Company (Vietnam), were designed as follows: forward inner primer (AGCACTTCACTACCAAATGAACC), reverse inner primer (CCTTCAATTCTGAAAAGTAGCTGAT), forward outer primer (AAAATATATTCCCCAAAAGCC), and reverse outer primer (TTTCTGACATTGTTCTTCGAGC). PCR was performed on a C1000 Thermal Cycler (Bio-Rad Laboratories, USA), with an initial denaturation at 95°C for 3 min, followed by 35 cycles of denaturation at 95°C for 30 sec, annealing at 60°C for 30 sec, and extension at 72°C for 30 sec, with a final extension at 72°C for 5 min. A negative control (distilled water) was used to ensure that contamination did not occur.

Finally, genotype identification was conducted by resolving the PCR products on a 1.5% agarose gel with Tris-acetate-EDTA 1X and a Phusa Genomics DNA ladder (Vietnam). There are three genotypes: AA, which represents the wild-type, and AC and CC, which are variant forms. The expected PCR product sizes were as follows: allele A (240 base pair [bp]); allele C (185 bp); and the outer primer forward-reverse fragment (377 bp). This method produced three distinct banding patterns corresponding to the three genotypes: AA (377 bp and 240 bp), AC (185 bp, 240 bp, and 377 bp), and CC (185 bp and 377 bp). To validate the T-ARMS-PCR results, two representative samples of AA genotype were sequenced at Phusa Genomics Co., Vietnam. The outer primer pair amplified a 377 bp segment, which was verified using Sanger sequencing to match the

expected sequence. The sequences were analyzed using SnapGene version 8.2.2 (GSL Biotech LLC, USA) to confirm that the amplified fragments corresponded to the target region of the rs5186.

Ethical approval

Our research project ensured compliance with the ethical principles of medical research. The study was approved by the Biomedical Research Ethics Committee of CTUMP under decision No. 23.153.HV/PCT-HĐĐĐ dated March 20th, 2023.

Data processing and analysis methods

All data were collected according to a standardized protocol and coded uniformly. The data were entered and checked for quality before analysis using Microsoft Excel (Microsoft Corporation, USA) and R software (version 4.5.2; R Foundation for Statistical Computing, Austria). Categorical variables were reported as frequencies, counts, and percentages. Differences between groups were tested using Pearson's chi-square or Fisher's exact tests, with $p < 0.05$ considered statistically significant.

Continuous quantitative variables were assessed before selecting the appropriate analytical method. For data with a normal distribution, the results are reported as mean (standard deviation [SD]) and compared using the Kruskal–Wallis rank-sum test or *t*-test. Data without a normal distribution, are expressed as median (interquartile range [IQR]) and were analyzed using the Wilcoxon rank-sum test. The genotype distribution in the control group was consistent with the Hardy–Weinberg equilibrium ($p = 0.08$), indicating reliable genotyping quality. Genotypic frequencies of rs5186 were analyzed using different inheritance models. Because the homozygous minor genotype (CC) was rare, a dominant model was applied in which the AC and CC genotypes were combined (AC + CC) and compared with the AA genotype. In addition, allelic analysis was conducted by comparing the distribution of the A and C alleles between the groups with and without hypertension. Associations between genotypes or alleles and the risk of hypertension were assessed using the chi-square or Fisher's exact test, as appropriate. Logistic regression models were used to evaluate the association between the rs5186 genotype and hypertension-related risk factors. Covariates were selected based on biological

Table 1. General characteristics of study participants

Characteristics	Hypertensive group (N = 65)	Non-hypertensive group (N = 65)	p
Age (years), mean (SD)	61.6 (12.8)	58.8 (10.3)	0.5*
BMI (kg/m ²), mean (SD)	24.23 (2.63)	23.01 (3.37)	0.002*
Sex, n (%)			1.0 [†]
Male	25 (38)	25 (38)	
Female	40 (62)	40 (62)	
Age (years), n (%)			0.6 [‡]
<40	2 (3)	0 (0)	
>60	36 (55)	32 (49)	
40–60	27 (42)	33 (51)	
BMI classification, n (%)			0.012[†]
Underweight–normal	22 (34)	39 (60)	
Overweight–obese	43 (66)	26 (40)	
Salt intake, n (%)			0.8 [†]
Yes	19 (29)	16 (25)	
No	46 (71)	49 (75)	
Smoking history, n (%)			1.0 [†]
Yes	9 (14)	8 (12)	
No	56 (86)	57 (88)	
Physical activity, n (%)			0.7 [†]
Yes	29 (45)	24 (37)	
No	36 (55)	41 (63)	

BMI=body mass index; SD=standard deviation

*Kruskal–Wallis rank sum test; [†]Pearson's chi-squared test; [‡]Fisher's exact test

relevance and univariate analyses ($p < 0.2$). Given the low frequency of the homozygous minor genotype, the AA genotype served as the reference group. To account for multiple testing, p -values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for both the unadjusted and adjusted models. Statistical significance was set at $p < 0.05$ after FDR correction.

RESULTS

General characteristics of the study population

The case group was older than the control group (61.6 [12.8] versus 58.8 [10.3]); however, the difference was not significant. The case group had a significantly higher prevalence of overweight and obesity than that of the control group (66% versus 40%, $p = 0.012$). Other factors, such as high salt intake, smoking habits, and physical activity, were not significantly different between the two groups ($p > 0.05$) (Table 1).

Characteristics of biochemical tests

Regarding lipid profiles indices across the entire study sample, the cholesterol levels ranged from 1.75 to 13.89 mmol/l, with a mean (SD) of 5.4 (1.6). TG levels ranged from 0.54 to 24.59 mmol/l, with a median (IQR) of 2 (1.2–3.0). HDL-C levels ranged from 0.66 to 2.36 mmol/l, with a mean (SD) of 1.2 (0.3), while LDL-C levels ranged from 1.52 to 8.19 mmol/l, with a mean (SD) of 3.4 (1.1). There were no statistically significant differences in lipid indices between the case and control groups (Figure 1).

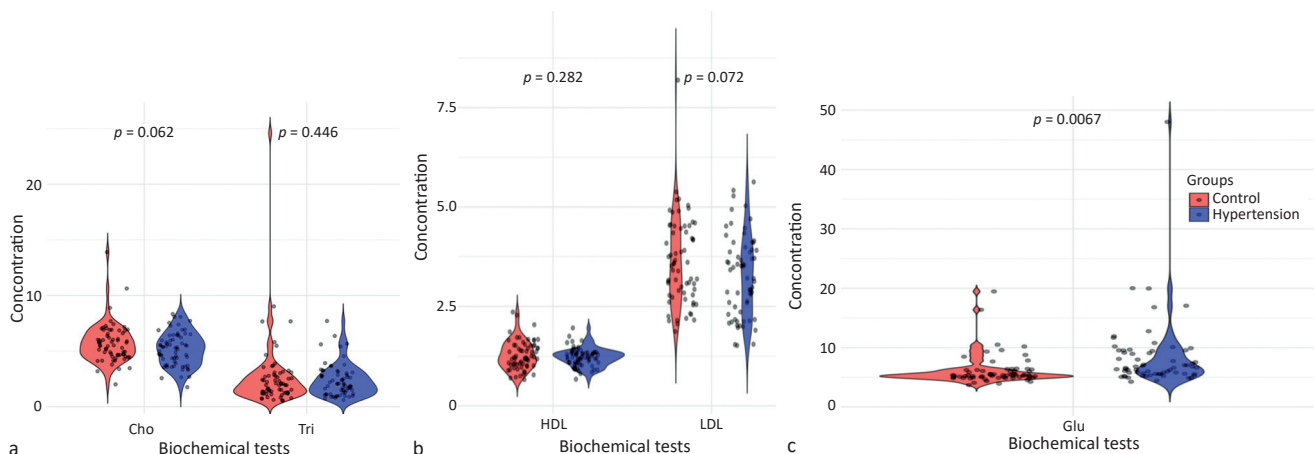


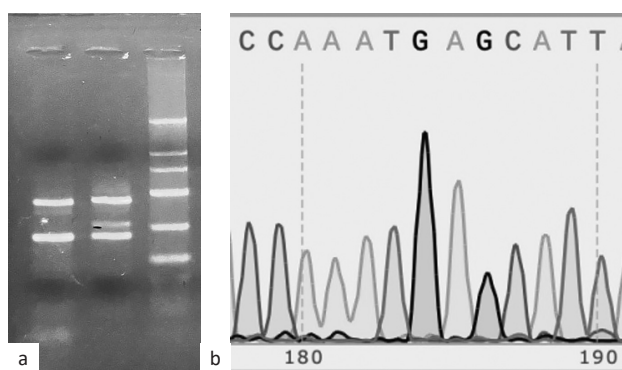
Figure 1. The characteristics of lipid profiles among hypertensive and non-hypertensive groups, cholesterol (Cho) and TGs (Tri) (a), HDL and LDL (b); and glucose (Glu) (c). HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglyceride

Table 2. Characteristics of biochemical tests in study participants

Tests	Hypertensive group, n (%) (N = 65)	Non-hypertensive group, n (%) (N = 65)	<i>p</i>
Glucose (mmol/l)			<0.001*
Abnormal	34 (52)	10 (15)	
Normal	31 (48)	55 (85)	
Cholesterol (mmol/l)			0.8*
Abnormal	34 (52)	38 (58)	
Normal	31 (48)	27 (42)	
TG (mmol/l)			1.0*
Abnormal	34 (52)	36 (55)	
Normal	31 (48)	29 (45)	
HDL-C (mmol/l)			0.5[†]
Abnormal	4 (6)	9 (14)	
Normal	61 (94)	56 (86)	
LDL-C (mmol/l)			1.0*
Abnormal	33 (51)	34 (52)	
Normal	32 (49)	31 (48)	

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride

*Pearson's chi-squared test; [†]Fisher's exact test

**Figure 2.** Gel electrophoresis of CC and AC genotypes with ladder from 100–2,000 bp (100, 250, 500, 750, 1,000, 2,000) (a); forward sequencing chromatogram showing a homozygous AA genotype at position 188 of rs5186, analyzed using SnapGene (b)

The glucose levels of the 130 patients (Figure 1) ranged from 3.69 to 48.02 mmol/l, with a median (IQR) of 5.8 (5.2–7.7). The glucose levels of case group were significantly higher than those of control group, with a significant difference ($p < 0.001$). Table 2 presents the biochemical characteristics of the study participants.

rs5186

On gel electrophoresis, the AA (377 bp and 240 bp) (not shown in Figure 2a) and CC genotypes had two

Table 3. Logistic regressions analysis of rs5186 (dominant model) and risk factors for hypertension

Variables	Adjusted OR (95% CI)	Unadjusted <i>p</i>	FDR- adjusted <i>p</i>
Genotypes			
(AC + CC) vs. AA	1.4 (0.6–2.8)	0.450	0.75
Smoking			
Yes vs. no	1.1 (0.4–3.2)	0.846	0.846
Physical activity			
Inactive vs. active	0.7 (0.3–1.6)	0.449	1.0
Salt intake			
Yes vs. no	1.2 (0.5–2.8)	0.606	0.758
Overweight/obesity			
Yes vs. no	3.0 (1.4–6.3)	0.003	0.015

CI=confidence interval; FDR=false discovery rate; OR=odds ratio

bands (377 bp and 185 bp), and the AC genotype had three bands (377 bp, 240 bp and 185 bp), as shown in Figure 2a (1st and 2nd lane). To verify the accuracy of the T-ARMS-PCR assay, two representative samples were subjected to Sanger sequencing at Phusa Genomics Co., Vietnam. Sequencing chromatograms confirmed that the amplified fragments corresponded to the target region of AGTR1 A1166C (rs5186). The forward sequencing chromatogram of a representative sample identified as AA using T-ARMS-PCR exhibited a clear single peak for adenine at position 188, consistent with the expected homozygous genotype (Figure 2b). Sequencing results confirmed that the amplified product matched the target gene region, supporting the reliability of the genotyping.

The AA genotype was the most prevalent (60%), with distributions of 55.4% and 64.6% in the case and control groups, respectively. The AC genotype accounted for 39.2% of all participants, with proportions of 43.1% and 35.4% in the case and control groups, respectively. The CC genotype was rare (0.8%), appearing in only one patient (1.5%) in the case group and none in the control group. The distributions of AA, AC, and CC genotypes did not differ significantly between the case and control groups ($p = 0.7$).

Association between rs5186 and hypertension risk factors

Multivariate logistic regression models were used to assess the association between the rs5186 polymorphism and hypertension risk, using the

Table 4. Logistic regression analysis of rs5186 (dominant model) and blood glucose and lipid profiles tests

Variables	Adjusted OR (95% CI)	Unadjusted <i>p</i>	FDR- adjusted <i>p</i>
Genotypes			
(AC + CC) vs. AA	1.4 (0.6–2.8)	0.434	0.651
Glucose (mmol/l)			
>6.5 vs. ≤6.5	6.0 (2.6–14.3)	<0.001	<0.001
TG (mmol/l)			
>1.88 vs. ≤1.88	0.8 (0.3–2.0)	0.724	0.724
Cholesterol (mmol/l)			
>5.2 vs. ≤5.2	0.5 (0.4–2.1)	0.382	0.764
HDL-C (mmol/l)			
<0.9 vs. ≥0.9	0.4 (0.1–1.6)	0.189	0.567
LDL-C (mmol/l)			
>3.4 vs. ≤3.4	1.3 (0.3–4.8)	0.678	0.814

CI=confidence interval; FDR=false discovery rate; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; OR=odds ratio; TG=triglyceride

dominant genetic model (AC + CC) versus AA, with AA as the reference group (Table 3).

A multivariate logistic regression model was constructed to assess the relationship between rs5186 and hypertension after adjusting for blood glucose and lipid profile. As shown in Table 4, patients with the AC genotype had an OR of 1.4 for developing hypertension compared to those with the AA genotype. However, this difference was not significant ($p = 0.651$). This indicated that after controlling for blood glucose and lipid profile tests, rs5186 was not significantly associated with the risk of hypertension.

Among the covariates included in the model, only high blood glucose levels (>6.5 mmol/l) were significantly associated with hypertension. Patients with the AC genotype and high blood glucose had a 6-fold higher risk of developing hypertension compared to those with the AA genotype and blood glucose levels ≤ 6.5 mmol/l (adjusted OR = 6.0; 95% CI: 2.6–14.3; $p < 0.001$). This finding indicates a strong association and highlights the critical role of impaired glucose metabolism in the risk of hypertension. In contrast, blood lipid parameters, including high TG (>1.88 mmol/l), total cholesterol (>5.2 mmol/l), low HDL-C (<0.9 mmol/l), and high LDL-C (>3.4 mmol/l) levels, were not significantly associated with hypertension in this model ($p > 0.05$).

DISCUSSION

The genotype distribution in the control group conformed to the Hardy–Weinberg equilibrium ($p = 0.08$), indicating reliable genotyping quality and no evidence of population stratification. This suggests that the control group was representative of the general population and that the observed genotype frequencies were not affected by systematic bias. In this study, the distribution of the AA, AC, and CC genotypes in the case group was 55.4%, 43.1%, and 1.5%, respectively. In the control group, the corresponding proportions were 64.6% and 35.4%, respectively, and no cases with the CC genotype were recorded. This indicates that the CC genotype had a minimal frequency, which is consistent with the results of previous studies conducted in other populations. For example, Yap et al¹⁵ studied 507 patients in Malaysia and reported AA, AC, and CC genotype frequencies of 86.8%, 12.6%, and 0.6%, respectively, in Malay individuals; 88.3%, 11.7%, and 0%, respectively, in Chinese individuals; and 88.1%, 11.9%, and 0%, respectively, in Indian individuals. Similarly, Feng et al¹⁵ reported a low prevalence of the CC genotype. In our study, only one patient carried the CC genotype, which may be attributed to the small sample size. However, this finding reflects the rarity of this genotype in the population.

The proportion of individuals with the AC genotype was higher in the case group than in the control group. This trend aligns with the findings of Chandra et al¹⁶ in North India, in which a study of 250 patients with hypertension and 250 controls reported AC genotype frequencies of 45.6% and 33.2%, respectively, and demonstrated a significant increase in the CC genotype in the hypertensive group ($p < 0.0001$), a pattern that was not observed in the control group. Similarly, a case-control study by Shahin et al⁹ at the Jordanian University Hospital of 108 patients with hypertension and 102 controls observed AC genotype frequencies of 34.3% and 31.4% in the case and control groups, respectively. These findings suggest that the AC genotype may be more prevalent in patients with hypertension than in controls, although the difference is not always significant.

Multivariate logistic regression using a dominant genetic model (AC + CC) versus AA showed that individuals with the AC genotype had a 1.4-fold higher risk of hypertension than those with the AA genotype; however, the difference was not significant.

Overweight/obesity was significantly associated with hypertension, and high blood glucose levels were strongly associated with it. FDR correction was applied to account for multiple testing, and significant associations remained for metabolic factors, whereas genetic associations remained non-significant.

Previous global studies have not provided consistent evidence of the relationship between rs5186 and hypertension across different populations. For example, Kikuya et al¹⁷ investigated 802 Japanese individuals aged ≥ 40 years and observed no relationship between rs5186 and hypertension- or atherosclerosis-related clinical parameters. In contrast, Parchwani et al⁶ examined 224 patients with primary hypertension and 257 healthy Indian controls and observed a significant difference in CC genotype frequencies between the hypertensive and control groups ($p = 0.013$). The CC genotype was associated with an increased risk of developing hypertension.⁶ Additionally, a case-control study by Semianiv et al¹⁰ involving 160 patients with primary hypertension and healthy participants reported an association between rs5186 and the risk of hypertension.

The differences in our results may reflect genetic variations across populations. Given the small sample size and convenience sampling used in this study, the generalizability of the results is limited. Therefore, this study may have been underpowered to detect the effects of these rare variants. Therefore, further research with larger sample sizes and more robust study designs is necessary to clarify the role of rs5186 in hypertension risk in the Mekong Delta region.

In addition to population differences, the lack of a significant association between rs5186 and hypertension in this study may have been influenced by environmental and metabolic factors that interacted with genetic susceptibility. High dietary sodium intake, obesity, and insulin resistance are well-established determinants of elevated BP, and may overshadow or modify the genetic contributions of *AGTR1* variants. Moreover, the strong association observed between hyperglycemia and hypertension in this cohort suggests that metabolic dysregulation plays a more dominant role in BP elevation than the effect of this polymorphism. Future studies incorporating gene-environment interaction analyses and longitudinal designs may help clarify these complex relationships.

This study had some limitations. First, the sample size was relatively small, which may have reduced

the statistical power to detect modest genetic effects and widened the CIs, leading to cautious interpretation of the lack of association between rs5186 and hypertension. Second, most participants were from the Kinh ethnic group, which may limit the generalizability of our findings to other populations. Third, to verify the accuracy of T-ARMS-PCR, several representative samples were analyzed using Sanger sequencing. Sequencing of an AA homozygous sample confirmed that the PCR product corresponded to the target region. However, the heterozygous (AC) samples showed unclear overlapping peaks, making genotype confirmation difficult. rs5186 has a low minor allele frequency in East Asian populations, which likely contributes to the limited number of CC genotypes observed in our sample and reduces the statistical power to detect associations. Finally, although FDR correction was applied, the study remains exploratory, and larger multi-ethnic studies with expanded sequencing validation are warranted.

In conclusion, this study did not identify a significant association between rs5186 and hypertension; however, the small sample size and low allele frequency may have limited its statistical power. Metabolic factors, particularly hyperglycemia and obesity, are strongly linked to hypertension, emphasizing the need for metabolic screening and lifestyle control. Larger multi-ethnic studies are needed to confirm these findings and explore gene-environment interactions.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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