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Research article

Physiological Role of Genetic Polymorphisms in the *AGTR1* Gene and Their Association with Inflammatory Cytokines in Blood Pressure Regulation

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Abstract: Hypertension is a major and largely asymptomatic contributor to cardiovascular morbidity, and genetic variation within the renin–angiotensin system is an important determinant of individual susceptibility. This case–control study examined the physiological contribution of two single-nucleotide polymorphisms (SNPs) in the angiotensin II type 1 receptor gene (AGTR1), rs5186 and rs2638360, to hypertension, together with the serum concentrations of the pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-17 (IL-17), in a cohort from Al-Qadisiyah Province, Iraq. Forty-eight hypertensive patients—stratified into mild, moderate, and severe subgroups—and 48 apparently healthy controls were genotyped by tetra-primer amplification refractory mutation system PCR (tetra-ARMS-PCR), and ELISA quantified serum cytokines. For rs5186, the A allele was associated with increased risk (OR = 2.14, $P < 0.01$), the C allele and the AC genotype showed protective odds ratios (OR = 0.47 and 0.37, respectively; $P < 0.05$), and the AA genotype was associated with increased risk (OR = 11.50, $P < 0.001$). For rs2638360, the AA genotype and the A allele were protective (OR = 0.055 and 0.20, respectively; $P < 0.0001$), whereas the AG and GG genotypes and the G allele conferred increased risk (OR = 4.86, 6.05, and 4.89, respectively; $P < 0.05$). Neither SNP was significantly associated with hypertension severity. Control genotype frequencies conformed to Hardy–Weinberg equilibrium for rs2638360 but deviated significantly for rs5186 ($P < 0.001$), so the rs5186 results require confirmation by an independent genotyping method. IL-6 and IL-17 were markedly elevated in patients (6.01 ± 0.42 and 2.87 ± 0.25 pg/mL, respectively; $P < 0.0001$) but did not differ across genotypes. These findings suggest that AGTR1 rs5186 and rs2638360 are associated with hypertension susceptibility in the Iraqi population and are consistent with a contributory role of vascular inflammation in disease pathophysiology, offering potential targets for population-specific management strategies.

Keywords: AGTR1; hypertension; inflammatory cytokines; renin–angiotensin system; single-nucleotide polymorphism

1. Introduction

Hypertension is a chronic, progressive disorder characterized by persistently elevated arterial pressure, conventionally defined by a systolic pressure of 140 mmHg or higher and/or a diastolic pressure of 90 mmHg or higher [1]. Because it is frequently asymptomatic, it is often described as a "silent killer". Recent World Health Organization (WHO) estimates reveal pronounced regional and

economic disparities in the global burden of hypertension, with the highest prevalence in the WHO Eastern Mediterranean Region (approximately 38%) and the lowest in the WHO Western Pacific Region (approximately 29%). The number of adults living with hypertension worldwide is reported to have risen sharply, from about 650 million in 1990 to roughly 1.4 billion, with much of the increase concentrated in low- and middle-income countries. Hypertension is associated with a broad spectrum of serious, often life-threatening comorbidities that impose a substantial burden on individuals, health systems, and society [2–5]. These include type 2 diabetes mellitus, dyslipidemia, obesity, renal injury, cardiovascular disease, stroke, retinopathy, cognitive decline, dementia, and obstructive sleep apnoea. Reflecting this burden, numerous regional and international bodies, among them the World Hypertension League, the International Society of Hypertension, the American Heart Association, the European Society of Hypertension, Hypertension Canada, the American Medical Association and the Pulmonary Hypertension Association—have prioritized hypertension control, and the WHO has set a target of a 30% reduction in hypertension prevalence between 2010 and 2030 [6]. Effective prevention, therefore, requires that the modifiable and non-modifiable risk factors for hypertension be addressed. Among the non-modifiable determinants, genetic factors influence individual susceptibility and may also affect disease prognosis [4].

Early genome-wide association studies (GWAS) identified only a small number of loci linked to blood pressure regulation [7, 8]. Subsequent investigations uncovered additional susceptibility regions across diverse populations [9–11], and larger studies progressively expanded the catalog of hypertension-associated loci [12, 13]. As human genomics has matured, increasingly powerful GWAS approaches have identified large numbers of variants that modestly increase hypertension risk [11, 14–17], although the individual effect of each variant is typically small, raising blood pressure by less than 1 mmHg [18]. The renin–angiotensin system (RAS) is a principal regulator of blood-pressure homeostasis, and genes encoding RAS components and their polymorphic variants are therefore strong candidates for studying genetic predisposition to hypertension [19]. One key component is the angiotensin II type 1 receptor (AGTR1), which is central to the development of hypertension and its comorbidities. The interaction of angiotensin II with AGTR1 triggers downstream responses including inflammation, oxidative stress, vasoconstriction, and sodium and water retention, ultimately elevating blood pressure [20]. Two SNPs in the *AGTR1* gene, rs5186 and rs2638360, have been repeatedly reported to be significantly associated with hypertension across populations of varied ethnic backgrounds [21]. rs5186 (A1166C) lies in the 3′-untranslated region. It has been linked to altered receptor expression through disruption of a microRNA (miR-155) binding site, whereas rs2638360 is an intronic variant whose functional consequences are less well defined but which may influence gene expression through effects on splicing or regulatory elements, or through linkage disequilibrium with nearby functional variants. According to WHO estimates for Iraq, a large proportion of the population aged 30–79 years is affected by hypertension, and around 45% of hypertension in this age group remained uncontrolled in recent estimates [22, 23]. Moreover, Iraq was ranked among the 25 countries with the highest hypertension-related mortality worldwide in 2021 [24]. Despite this burden, the influence of the rs5186 and rs2638360 variants on hypertension in the Iraqi population remains markedly under-researched. Accordingly, the present study was designed to clarify the physiological role of these two SNPs in a case–control cohort drawn from Al-Qadisiyah Province, Iraq, and to evaluate the serum concentrations of the pro-inflammatory cytokines IL-6 and IL-17 in the enrolled participants.

2. Materials and Methods

2.1 Study design and participants

This case–control study enrolled 96 adults: 48 hypertensive patients and 48 apparently healthy controls. Patients were recruited consecutively from attendees of Al-Qadisiyah Hospital between January and June 2025. Written informed consent was obtained from every participant before enrolment. The study was conducted in accordance with the Declaration of Helsinki and was ethically approved by the Institutional Review Board of the Faculty of Medicine, University of Al-Qadisiyah.

2.2 Blood pressure measurement

Blood pressure was measured in all participants after a rest period of at least five minutes. Measurements were performed by trained medical staff, following standardized procedures, using an automated sphygmomanometer (Omron Healthcare, Kyoto, Japan). Readings were classified according to established guidelines as normal (systolic blood pressure, SBP < 140 mmHg and diastolic blood pressure, DBP < 90 mmHg), mild hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg), moderate hypertension (SBP 160–179 mmHg and/or DBP 100–109 mmHg), and severe hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg). On this basis, the hypertensive group was further sub-stratified into mild, moderate, and severe subgroups. When the systolic and diastolic readings corresponded to different grades, the higher grade was assigned, in accordance with the 2020 ISH guideline [1]. The overall research framework is summarised in Figure 1.

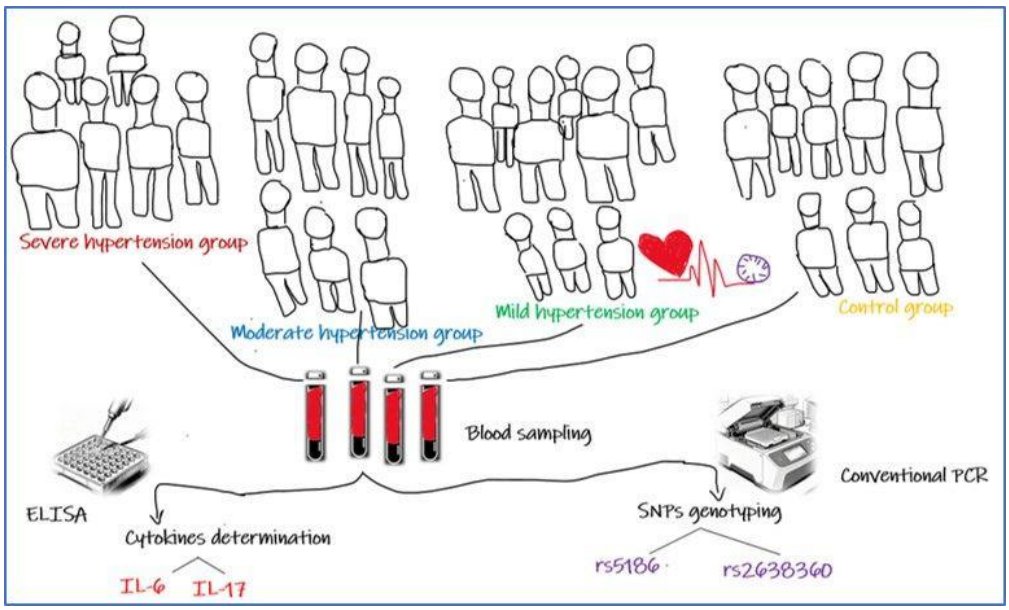


Figure 1. Schematic overview of the research framework. Patients were categorized into mild, moderate, and severe hypertension subgroups according to the 2020 International Society of Hypertension Global Hypertension Practice Guidelines [1].

2.3 Blood sampling

Six milliliters of venous blood were drawn from each participant. Three milliliters were collected into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes for genomic DNA extraction, and the remaining 3 mL was transferred into clot-activator (serum-separator) tubes for subsequent cytokine quantification.

2.4 Genomic DNA isolation

Genomic DNA was extracted from the EDTA blood using the QIAamp DNA Blood Kit (Qiagen, Germany) according to the manufacturer's protocol (Figure 2). The purity and concentration of the isolated DNA were determined with a NanoDrop 2000 UV spectrophotometer (Thermo Fisher Scientific, USA); an absorbance of 1.0 at 260 nm corresponds to approximately 50 μg/mL of double-stranded DNA. The A260/A280 ratio assessed DNA purity; values near 1.8 indicate high-quality, contaminant-free DNA. DNA integrity was further verified by electrophoresis on a 1% agarose gel and visualization under a UV transilluminator (Cleaver Scientific, UK).

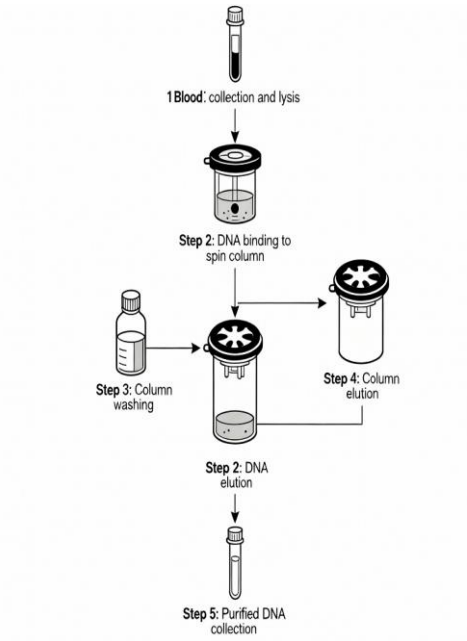


Figure 2. Workflow for genomic DNA isolation from participant blood samples using the QIAamp DNA Blood Kit (Qiagen, Germany). The schematic was generated using an artificial-intelligence tool (Perplexity AI).

2.5 Selection of single-nucleotide polymorphisms

Two SNPs located in the *AGTR1* gene, with dbSNP accession numbers rs5186 and rs2638360, were investigated. The flanking nucleotide sequences of both SNPs were retrieved from the NCBI dbSNP database (https://www.ncbi.nlm.nih.gov/snp/).

2.6 Primer design and synthesis

For each SNP, a tetra-primer ARMS-PCR primer set was designed using the dedicated online tool Primer1 (http://primer1.soton.ac.uk/primer1.html) [25]. Primer specificity and accuracy were verified in silico using the NCBI Primer-BLAST tool. All primer sets were chemically synthesized and validated by Integrated DNA Technologies (IDT), USA. The primer sequences are listed in Table 1.

Table 1. Tetra-primer ARMS-PCR primer sets for the SNPs rs5186 and rs2638360.

SNP	Primer sequence (5′→3′)	Tm (°C)	PCR product size
rs5186	Forward inner (A-allele): TGCAGCACTTCACTACCAAATGAACA	66	A allele: 201 bp
	Reverse inner (C-allele): TTTCTCCTTCAATTCTGAAAAGTAGCTGAG	65	C allele: 172 bp
	Forward outer: TCAGATAATGTAAGCTCATCCACCAAGA	65	Control fragment: 317 bp
	Reverse outer: CACATTCATCGAGTTTCTGACATTGTTC	65	
rs2638360	Forward inner (G-allele): AATTCTGTAAGATTTTCTTTAGTTTTCAAG	58	G allele: 203 bp
	Reverse inner (A-allele): ATGCAATGGTGAAATGTTTATCATGAT	63	A allele: 225 bp
	Forward outer: TTTCTTAAAATTGTGAAAAGAAGTACCC	60	Control fragment: 371 bp
	Reverse outer: TATCCAAACCTTATCAGTGACATACAAT	60	

Inner and outer primer sequences flank the SNP position within the *AGTR1* gene.

Table 2. Reaction composition for tetra-primer ARMS-PCR genotyping of rs5186 and rs2638360.

Component	Volume (μL)
DNA template (100 ng/μL)	3.0
PCR Master Mix, 2× (Thermo Scientific™)	12.5
Inner forward primer (10 pmol/μL)	2.0
Inner reverse primer (10 pmol/μL)	2.0
Outer forward primer (10 pmol/μL)	1.5
Outer reverse primer (10 pmol/μL)	1.5
Nuclease-free water	2.5
Total volume	**25.0**

2.8 Determination of serum IL-6 and IL-17

Serum concentrations of IL-6 and IL-17 were measured by enzyme-linked immunosorbent assay (ELISA) using human IL-6 and IL-17 SimpleStep ELISA kits (Fine Biotech, China) according to the manufacturer's instructions. The IL-6 assay had a working range of approximately 4.688–300 pg/mL and a sensitivity of 2.813 pg/mL, whereas the IL-17 assay had a working range of approximately 31.25–2000 pg/mL and a sensitivity of 18.75 pg/mL.

2.9 Statistical analysis

Data were analyzed using SPSS v25.0. Continuous variables are summarised as mean ± standard deviation. Groups were compared using one-way analysis of variance, independent-samples t-tests, and the chi-square test, as appropriate. For each SNP, genotype associations were evaluated by comparing the specified genotype against the pooled remaining genotypes in a 2 × 2 table, and the overall genotype distribution was additionally compared between groups using a 2 × 3 chi-square test; allele associations were derived from 2 × 2 allele-count tables. The assumptions of the parametric tests were checked before their application. A P value below 0.05 was considered statistically significant. Genotype and allele associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs); ORs below 1 indicate a protective effect, and those above 1 indicate increased risk. Hardy–Weinberg equilibrium in the control group was tested for each SNP with a chi-square goodness-of-fit test (one degree of freedom) comparing observed genotype counts with those expected from the allele frequencies. Because multiple genotype, allele, and cytokine comparisons were performed across the two SNPs, no formal correction for multiple testing was applied, and the individual associations are regarded as exploratory; for reference, a Bonferroni-corrected threshold for the principal comparisons is approximately $\alpha = 0.005$. No a priori sample-size calculation was performed, and a post hoc appraisal of statistical power is provided in the Discussion. Serum cytokine concentrations are reported as the patient-level and control-level mean ± standard deviation (n = 48 per group) and were compared between groups by independent-samples t-test. Data were visualized as histograms and waffle charts using GraphPad Prism v8.0.

3. Results and Discussion

3.1 Distribution of hypertension severity

The distribution of hypertension severity within the patient group is shown as a waffle chart in Figure 3. Mild hypertension was the most common category (41.66%), moderate hypertension the least common (25.00%), and severe hypertension intermediate (33.33%). Despite these numerical differences, the distribution did not differ significantly ($P > 0.05$).

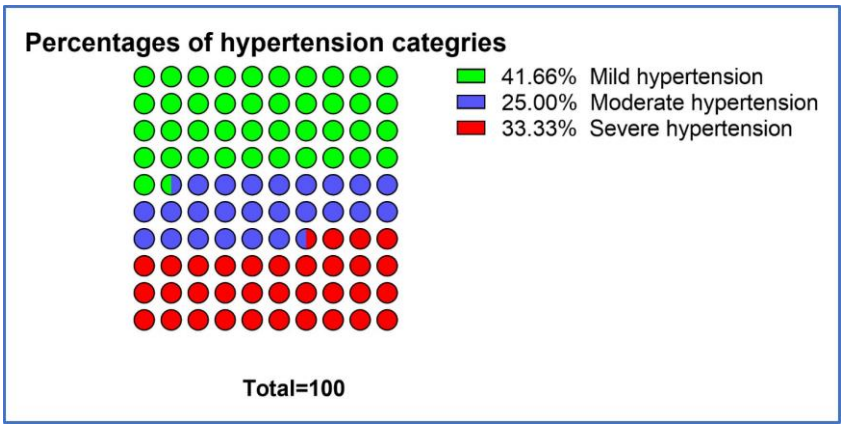


Figure 3. Waffle chart showing the distribution of hypertension severity within the patient group (GraphPad Prism v8.0). Values represent the percentage of patients in each severity category (total = 100%), not absolute counts.

3.2 Tetra-ARMS-PCR banding patterns

Tetra-primer ARMS-PCR produced the expected banding patterns for genotyping of both SNPs (Figures 4 and 5). For rs5186, three fragments were observed across the cohort—201 bp (A allele), 172 bp (C allele), and 317 bp (control)—whereas for rs2638360, the fragments were 203 bp (G allele), 225 bp (A allele), and 371 bp (control).

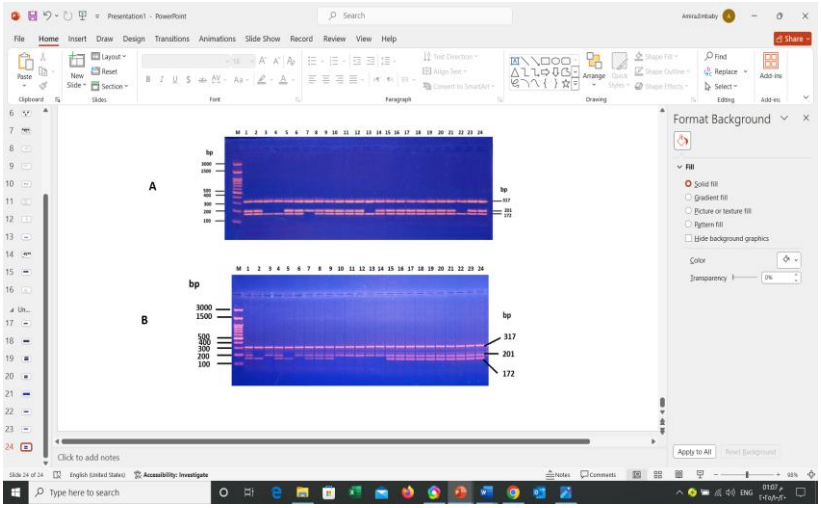


Figure 4. Agarose gel electrophoresis (1.5%) of tetra-ARMS-PCR products for rs5186 genotyping. Representative samples from healthy controls (A) and patients (B). M, DNA ladder; lanes 1–24, PCR products showing the three possible fragments: A allele (201 bp), C allele (172 bp), and control (317 bp).

3.3 Genotype and allele distribution of rs5186

The genotype and allele distributions for rs5186 are presented in Table 3. Both the AA genotype and the A allele were significantly more frequent in patients than in controls ($P < 0.0001$), whereas the AC genotype was more frequent in controls ($P = 0.028$); the CC genotype did not differ significantly between groups ($P > 0.05$). The C allele was likewise over-represented among controls. Based on the reported odds ratios, the AA genotype was associated with a markedly increased risk of hypertension (OR = 11.50; 95% CI 2.47–53.52; $P < 0.0001$), consistent with its higher frequency among patients, whereas the AC genotype showed a protective effect (OR = 0.3684; 95% CI 0.1494–0.9085; $P < 0.05$). The CC genotype (OR = 0.4545; 95% CI 0.1271–1.6256; $P > 0.05$) was neither protective nor risk-conferring, as its confidence interval crossed unity. At the allelic level, the A allele was associated with increased risk (OR = 2.1429; 95% CI 1.2030–3.8171; $X^2 = 6.77$; $P = 0.009$), whereas the C allele was protective (OR = 0.4667; 95% CI 0.2620–0.8313; $X^2 = 6.77$; $P = 0.009$). The AA genotype thus represented

the highest-risk genotype for rs5186, in agreement with the risk direction of the A allele. However, because the rs5186 control genotypes departed from Hardy–Weinberg equilibrium and the risk direction of the A allele is opposite to that most often reported for A1166C, these rs5186 findings should be regarded as provisional and require confirmation by an independent genotyping method (see Section 3.4 and the study limitations).

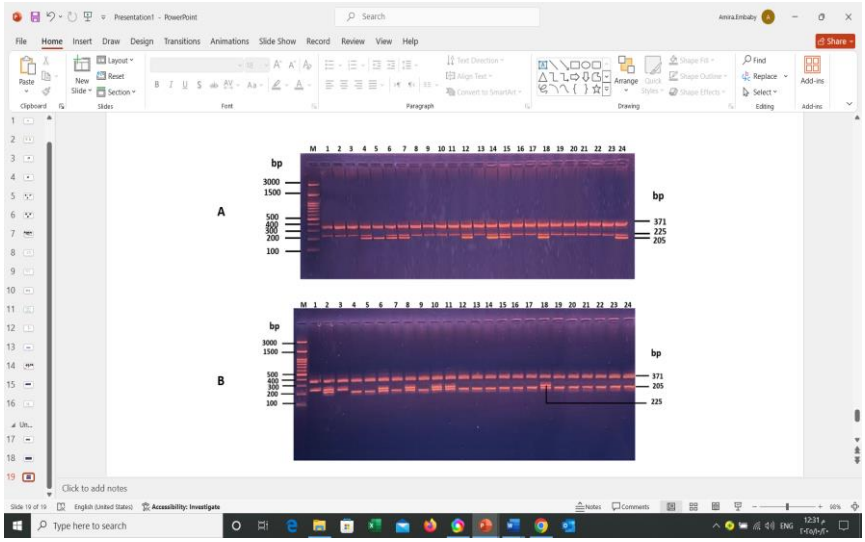


Figure 5. Agarose gel electrophoresis (1.5%) of tetra-ARMS-PCR products for rs2638360 genotyping. Representative samples from healthy controls (A) and patients (B). M, DNA ladder; lanes 1–24, PCR products showing the three possible fragments: G allele (203 bp), A allele (225 bp), and control (371 bp).

Table 3. Genotype and allele distribution of rs5186 among the study cohorts.

Genotype/Allele	Category	Control n (%)	Patients n (%)	X^2 / P value	OR	95% CI
Genotypes	AA	2 (4.16)	16 (33.33)	13.4 / <0.0001 (HS)	11.50	2.47–53.52
	AC	38 (79.16)	28 (58.33)	4.84 / 0.028 (S)	0.3684	0.1494–0.9085
	CC	8 (16.66)	4 (8.33)	1.52 / 0.217 (NS)	0.4545	0.1271–1.6256
Alleles	A	42 (43.75)	60 (62.50)	6.77 / 0.009 (HS)	2.1429	1.2030–3.8171
	C	54 (56.25)	36 (37.50)	6.77 / 0.009 (HS)	0.4667	0.2620–0.8313

S, significant (P < 0.05); HS, highly significant; NS, not significant. OR, odds ratio; CI, confidence interval.

3.4 Genotype and allele distribution of rs2638360

For rs2638360, the AA genotype and the A allele were markedly more frequent in controls than in patients, whereas the AG and GG genotypes and the G allele predominated among patients (P < 0.05; Table 4). The AA genotype (OR = 0.0545; 95% CI 0.0168–0.1773; P < 0.0001) and the A allele (OR = 0.2047; 95% CI 0.1083–0.3868; P < 0.0001) were strongly protective. In contrast, the AG genotype (OR = 4.8571; 95% CI 2.0459–11.5312; P < 0.0001), the GG genotype (OR = 6.0526; 95% CI 1.2494–29.3218; P = 0.014) and the G allele (OR = 4.8857; 95% CI 2.5850–9.2340; P < 0.0001) all conferred increased risk. The protective role of the AA genotype and A allele was supported by large chi-square values (X^2 = 30.78 and 25.41, respectively), while the risk associations of the AG and GG genotypes and G allele were reflected in chi-square values of 13.52, 6.09, and 25.41, respectively. Genotype frequencies in the control group were tested for Hardy–Weinberg equilibrium (HWE). For rs2638360, the observed control genotypes (AA = 30, AG = 16, GG = 2) closely matched those expected under HWE (30.1, 15.8, and 2.1; chi-square = 0.01, df = 1, P = 0.94). For rs5186, however, the observed control genotypes (AA = 2, AC = 38, CC = 8) deviated markedly from the HWE expectation (AA = 9.2, AC = 23.6, and CC = 15.2; chi-square = 17.8, df = 1, P < 0.001), reflecting a large excess of heterozygotes (observed heterozygosity 0.79 versus 0.49 expected). Such heterozygote excess is a recognized signature of genotype mis-scoring in allele-specific assays; the rs5186 results are therefore interpreted with caution and require confirmation by an independent method (see the study limitations).

Table 4. Genotype and allele distribution of rs2638360 among the study cohorts.

Genotype/Allele	Category	Control n (%)	Patients n (%)	X^2 / P value	OR	95% CI
Genotypes	AA	30 (62.50)	4 (8.33)	30.78 / <0.0001 (HS)	0.0545	0.0168–0.1773
	AG	16 (33.33)	34 (70.83)	13.52 / <0.0001 (HS)	4.8571	2.0459–11.5312
	GG	2 (4.16)	10 (20.83)	6.09 / 0.014 (S)	6.0526	1.2494–29.3218
Alleles	A	76 (79.16)	42 (43.75)	25.41 / <0.0001 (HS)	0.2047	0.1083–0.3868
	G	20 (20.83)	54 (56.25)	25.41 / <0.0001 (HS)	4.8857	2.5850–9.2340

S, significant (P < 0.05); HS, highly significant. OR, odds ratio; CI, confidence interval.

3.5 Genotypes in relation to hypertension severity

The distribution of genotypes across the hypertension-severity subgroups is shown in Figures 6 and 7. No statistically significant association between genotype and severity was detected for either SNP, and the subgroups were small; the following observations are therefore descriptive only and are not interpreted mechanistically. For rs5186, a high proportion of patients carrying the AA genotype had severe hypertension (56.25%), whereas the AC genotype was most frequent among patients with mild hypertension; a high proportion of CC carriers also presented with severe hypertension. Overall, however, no statistically significant association between rs5186 genotype and severity was detected.

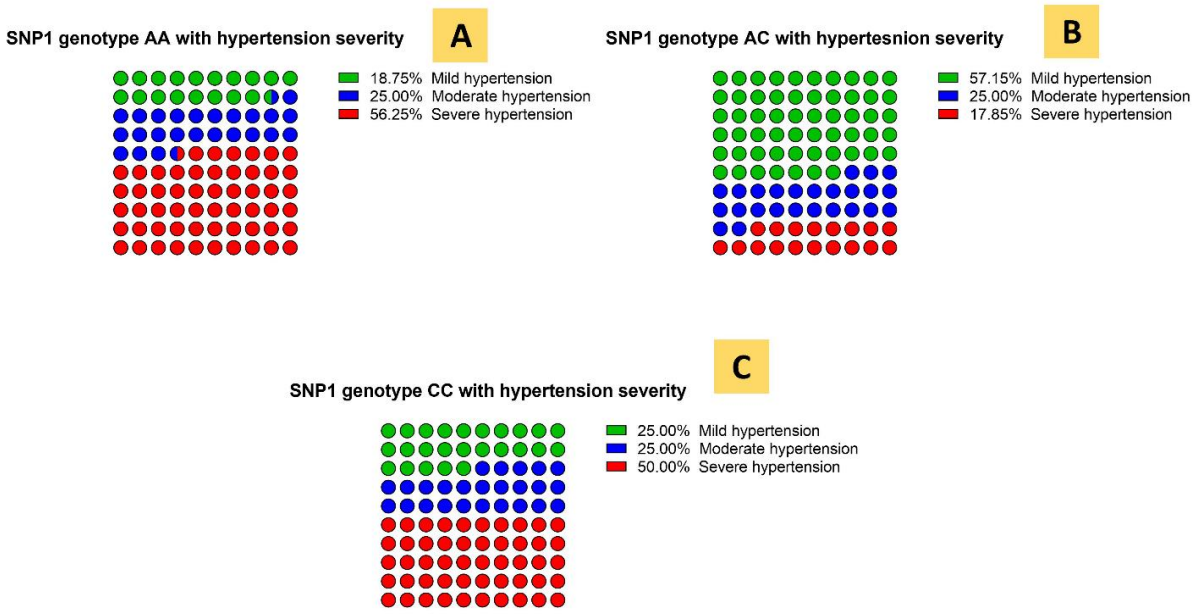


Figure 6. Waffle chart of hypertension severity in relation to rs5186 genotypes: AA (A), AC (B), and CC (C).

For rs2638360, the numerical distribution of severity across genotypes did not reach statistical significance. Given the small number of patients in each subgroup (for example, only four patients carried the rs2638360 AA genotype), these comparisons were underpowered, and the apparent differences between subgroups are not interpreted further.

3.6 Serum cytokine levels

Serum concentrations of IL-6 and IL-17 were significantly higher in patients than in controls (6.01 ± 0.42 and 2.87 ± 0.25 pg/mL, respectively; P < 0.0001; Figure 8), consistent with a role for these pro-inflammatory cytokines in the vascular inflammation and endothelial dysfunction that underlie hypertension.

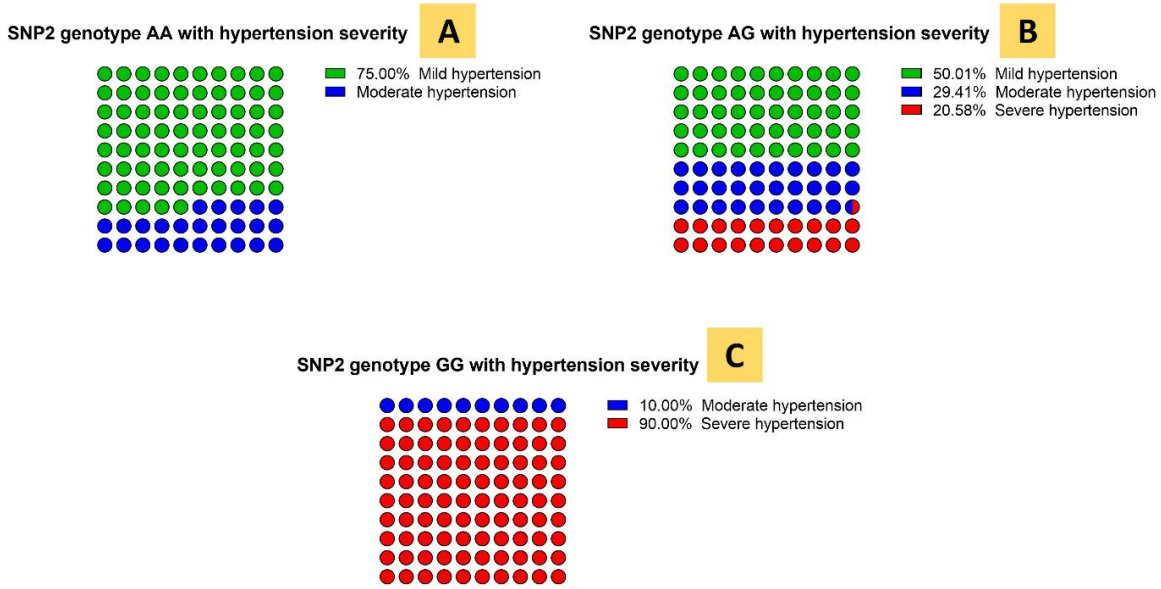


Figure 7. Waffle chart of hypertension severity in relation to rs2638360 genotypes: AA (A), AG (B), and GG (C).

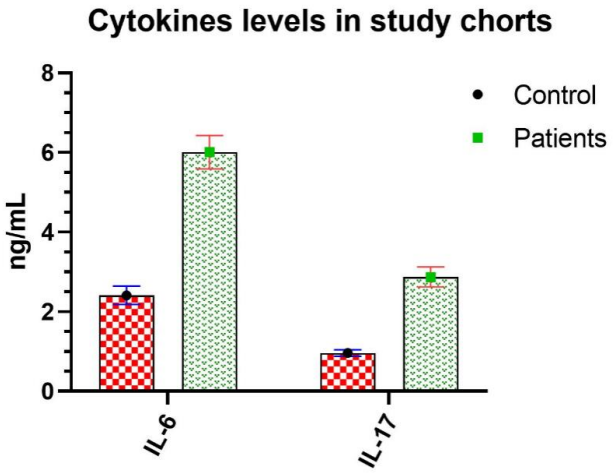


Figure 8. Serum concentrations of IL-6 and IL-17 in the patient and control groups. Concentrations are expressed in pg/mL. Values are the patient-level mean ± standard deviation (n = 48 patients and n = 48 controls) and were compared by independent-samples t-test; $P < 0.0001$.

3.7 Genotypes in relation to cytokine levels

No significant differences in IL-6 or IL-17 concentrations were observed across the genotypes of rs5186 (AA, AC, CC) or rs2638360 (AA, AG, GG) ($P > 0.05$; Figure 9). No association between genotype and cytokine concentration was detected; however, cytokines were measured in patients only and were divided across three genotype groups, so the study was not powered to exclude such an association, and no mechanistic inference can be drawn from this null result.

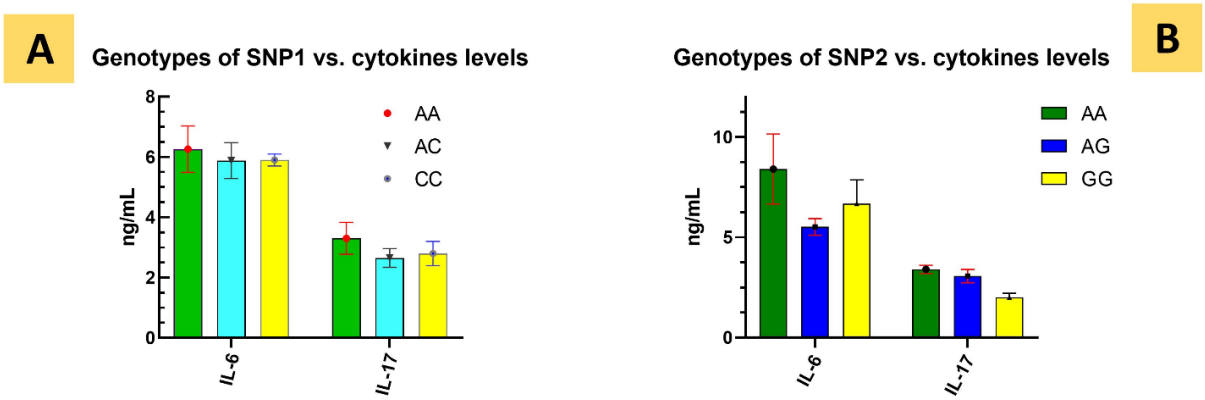


Figure 9. Serum IL-6 and IL-17 concentrations in the patient group, by genotype: rs5186 (A) and rs2638360 (B). Values are the patient-level mean ± standard deviation; differences across genotypes were not statistically significant (P > 0.05).

3.8 AGTR1 gene interaction network

To place the two variants in a broader molecular context, an *AGTR1* gene-interaction network was constructed using GeneMANIA (http://genemania.org) (Figure 10). The network highlights the functional centrality of AGTR1 and the diversity of its molecular partners—including AGT, AGTR2, AGTRAP, MAS1, CALB2, MAPK1 and ARRB1/2—implicating the receptor in signal transduction, receptor cross-talk and the regulation of vascular tone. These connections underscore the potential role of AGTR1 in broader physiological and disease processes that predispose individuals to hypertension and identify candidate targets for further study.

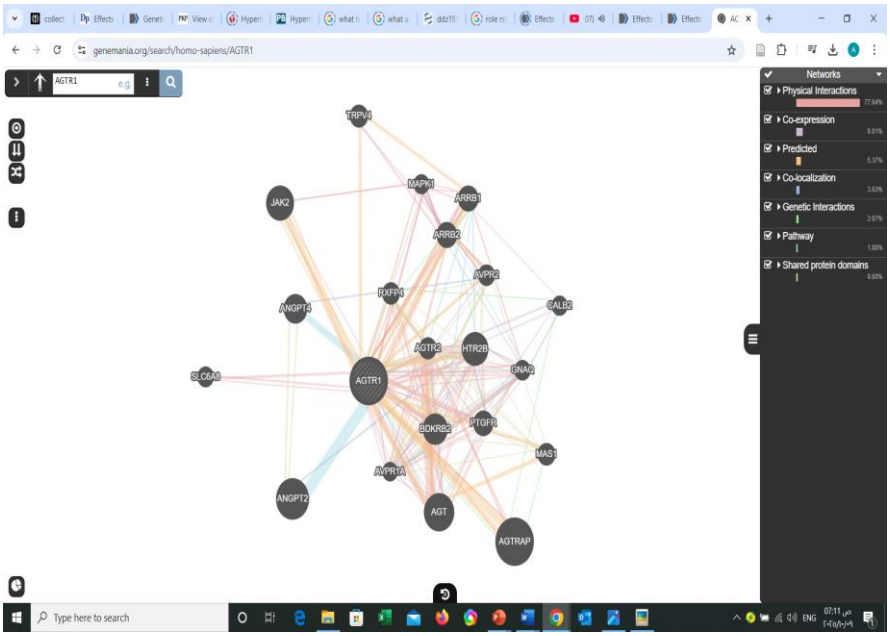


Figure 10. AGTR1 gene-interaction network generated with GeneMANIA (http://genemania.org). AGTR1 (highlighted in red, circled) is shown as the central node, with direct and indirect connections to signaling and regulatory partners.

3.9 Discussion

This study contributes to the growing body of evidence on the association with hypertension of two loci—rs5186 and rs2638360—in the *AGTR1* gene, which encodes the angiotensin II type 1 receptor, a pivotal mediator of blood-pressure regulation within the renin–angiotensin system. Variation in this receptor influences vascular tone, sodium handling, and sympathetic activity, thereby modulating susceptibility to

hypertension. The present cohort was drawn from Al-Qadisiyah Province, Iraq, a population in which the effects of these SNPs on hypertension have been little studied. Earlier work in Baghdad reported that the AA genotype of rs5186 was more common in normotensive than hypertensive individuals (68% vs 42%), with the AC and CC genotypes more frequent among patients [26]. In Karbala, genotype frequencies of 53.33% (AA), 40.22% (AC), and 5.43% (CC) were observed, with no significant effect of genotype on severity—possibly reflecting multifactorial interactions with other genetic or environmental modifiers of vascular remodelling and endothelial function [27]. In a Ukrainian cohort, the C allele was associated with hypertension, potentially through altered receptor activity and downstream signaling that heightens vasoconstriction and sodium retention [28]. In contrast, no significant association was found in an indigenous Arctic population, possibly owing to distinct environmental or epigenetic regulation of *AGTR1* expression [29]. Several studies have linked rs5186 to blood pressure through changes in angiotensin II receptor affinity or signal transduction [30, 31], although a Russian study found no association between rs5186 and obesity, a comorbidity that aggravates hypertension via inflammatory and metabolic mechanisms [32]. Hypertension in hypercholesterolaemic patients has also been associated with the C allele, suggesting an interplay among lipid metabolism, vascular inflammation, and AGTR1 function [33].

Consistent with our findings, the A allele was predominant in hypertensive subjects (97.5%) compared with normotensive subjects (80%) in an Egyptian population, suggesting effects on receptor expression or signalling efficiency that influence vascular resistance [34]. A meta-analysis including South African ethnic groups corroborated the association of rs5186 with increased hypertension risk, reinforcing the gene's physiological relevance across diverse populations [35]. In Al-Diwaniyah, Iraq, the AA genotype was associated with coronary heart disease as a hypertensive comorbidity, implicating AGTR1 in cardiac remodelling and endothelial dysfunction [36], and in a Thai cohort, the AC and CC genotypes were linked to higher systolic and diastolic pressures, possibly through enhanced receptor-mediated vasoconstrictive signalling [37]. Fewer studies have addressed rs2638360. The G allele was identified as an important predictor of hypertension in the Chinese Hani and Yi minorities, indicating a role in blood-pressure regulation [38]. Because salt sensitivity is a key predisposing factor for hypertension, several studies have examined the influence of rs2638360 and related loci on blood pressure salt sensitivity [39–45]. Such associations are likely mediated by SNP-dependent modulation of AGTR1 function, which affects renal sodium reabsorption, vascular smooth muscle contraction, and, consequently, blood volume and vascular resistance—central mechanisms in salt-sensitive hypertension. Nonetheless, the relationship between *AGTR1* variants (rs5186 and rs2638360) and hypertension susceptibility remains incompletely defined across populations, and larger studies incorporating functional analyses are warranted. Regarding inflammation, numerous studies have implicated the pro-inflammatory cytokines IL-6 and IL-17 in the pathophysiology of hypertension [46–51]. Consistent with our results, hypertensive patients typically exhibit elevated levels of these cytokines compared with normotensive individuals [52–54]. IL-6 and IL-17 promote vascular inflammation, endothelial dysfunction, and oxidative injury, contributing to vasoconstriction and vascular remodelling, and can amplify the hypertensive actions of angiotensin II, thereby linking immune activation to blood-pressure regulation. Recent evidence underscores the importance of controlling inflammatory cytokine levels to mitigate their adverse effects on hypertension development and end-organ damage [51, 55]. IL-17 in particular is regarded as a cardiovascular risk factor and a contributory variable in disease progression [56–60].

Several limitations should be considered when interpreting these findings. First, the sample size was modest (48 patients and 48 controls) and was not based on an a priori power calculation; a post hoc appraisal indicates limited power to detect small-to-moderate genotypic effects, so non-significant results—including the absence of genotype–severity and genotype–cytokine associations—cannot exclude true effects, and the significant associations require replication in larger cohorts and carry a corresponding risk of false-positive findings. Second, no formal correction for multiple testing was applied; under a conservative Bonferroni adjustment for the comparisons performed, some individually significant results would no longer reach significance, so they should be regarded as exploratory. Third, baseline characteristics (age, sex, body-mass index, smoking, diabetes, lipid profile, medication, and family history) and the age- and sex-matching of controls were not available for the present analysis, and the associations were not adjusted for these potential

confounders by multivariable logistic regression; residual confounding therefore cannot be excluded. Fourth, and most importantly for rs5186, the control genotype distribution departed significantly from Hardy–Weinberg equilibrium, with a heterozygote excess characteristic of genotype mis-scoring in allele-specific assays, and the risk direction of the A allele is opposite to that most commonly reported for A1166C, in which the C allele is conventionally the risk allele; the rs5186 genotyping therefore requires confirmation by an orthogonal method (for example, Sanger sequencing of a representative subset spanning all three genotypes) before the rs5186 associations can be considered reliable. Finally, no functional assays were performed, so the receptor-level and inflammatory mechanisms discussed above are inferred from the literature rather than demonstrated here; accordingly, the results describe statistical associations rather than causal relationships.

4. Conclusions

In this case–control study from Al-Qadisiyah Province, the *AGTR1* variants rs5186 and rs2638360 were significantly associated with hypertension susceptibility. For rs5186, the A allele conferred risk, while the C allele and the AC genotype were protective; for rs2638360, the AA genotype and A allele were protective (although the rs5186 genotyping requires independent confirmation, as discussed), while the AG and GG genotypes and the G allele conferred risk. Neither SNP was significantly associated with disease severity. Serum IL-6 and IL-17 were markedly elevated in patients but did not vary with genotype, although the study was not powered to exclude an effect on systemic cytokine levels. Together, these results are consistent with an association of *AGTR1* genetic variation—and of vascular inflammation—with hypertension and highlight potential targets for population-specific prevention and management strategies. The principal limitation is the modest sample size, which reduces the statistical power to detect subtle physiological effects of the studied variants. In addition, analyzing only two polymorphisms and two cytokines provides a limited view of the complex molecular and immunological pathways underlying hypertension. A broader panel of genetic and inflammatory biomarkers would afford a fuller understanding of the immuno-physiological processes driving disease progression and treatment response. Future studies should employ larger samples to reduce statistical bias and strengthen the detection of genetic associations. Integration with international genomic databases would facilitate the identification of additional loci relevant to hypertension susceptibility and to the regulation of inflammatory cytokines. A comprehensive investigation of these loci in Iraqi populations would provide further physiological and molecular insights into the pathogenesis of this largely asymptomatic disorder and could inform improved strategies for its prevention and management.

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