Vascular Health and Risk Management

Dovepress
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ORIGINAL RESEARCH

Investigating the Role of Gene Polymorphisms in Hypertension: Evidence from the Jordanian Population

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Purpose: Hypertension (HTN) is a complex disorder regulated by multiple physiological systems. Each individual's underlying genetic architecture strongly influences inter-individual variability in therapeutic responses to HTN. Consequently, identifying candidate genes that contribute to the genetic basis of HTN remains a significant challenge. This study aims to investigate the association between eleven polymorphisms across eight candidate genes and HTN in the Jordanian population.

Patients and Methods: This study included 200 patients with hypertension from Jordan and 224 healthy controls. Whole blood samples were collected from each participant, followed by the extraction of genomic DNA. The distribution of polymorphisms in the genes VEGFA, NAT2, TANC2, NR3C2, PROX1, PTGER3, TLE1, and PRKCA was investigated. Haplotype, genotype, and allele frequencies were analyzed using the SNPStats web tool.

Results: In the Jordanian population, significant differences were observed in the frequency of the A/A genotype of rs699947 in VEGFA and the G/A genotype of rs2429427 in TANC2 ($P = 0.006$ and 0.042, respectively) between healthy individuals and those with hypertension. No significant associations were detected for the other SNPs analyzed with hypertension incidence. Additionally, significant differences were noted in the codominant and recessive models of VEGFA rs699947, the recessive model of NAT2 rs1041983, the dominant and overdominant models of TANC2 rs2429427, and the overdominant model of NR3C2 rs5522 between the groups. Overall, the genotype distributions of the VEGFA and TANC2 genes differed significantly between healthy individuals and those with hypertension.

Conclusion: These findings highlight the potential of incorporating genetic profiling into clinical practice to enable more precise, genotype-guided hypertension management, paving the way for personalized therapeutic strategies in affected populations.

Keywords: hypertension, VEGFA, NAT2, TANC2, polymorphisms

Introduction

Hypertension (HTN), often referred to as the "silent killer", is defined as a persistent elevation in systolic and/or diastolic blood pressure (BP) of 140/90 mmHg or higher.[1–3] Hypertension is the leading cause of mortality associated with lifestyle factors and is linked to an increased risk of myocardial infarction, stroke, heart failure, and renal disease.[2,4–7] Hypertension has emerged as a major public health issue and a significant national and global concern, as uncontrolled HTN imposes a substantial economic burden on national budgets, healthcare systems, and households.[1,3,5,8] HTN is a multifactorial condition influenced by various genetic and epigenetic factors, as well as environmental and lifestyle factors, including nutrition, smoking habits, and physical activity.[9–13] Although blood pressure exhibits a considerable degree of heritability, identifying the genetic factors that contribute to blood pressure variability and the risk of hypertension in the general population remains a significant challenge.[1,4,5,9,14] Despite the recognition of multiple risk factors, the pathophysiology of hypertension remains unclear. The incidence continues to rise, and long-term treatment often proves ineffective.[15]

Received: 24 April 2025
Accepted: 16 August 2025
Published: 3 September 2025

Human vascular endothelial growth factor (VEGF) is a potent regulator of both physiological and pathological angiogenesis, and it is implicated in various immunological and inflammatory processes in vascularized organs, such as the kidney.[16,17] It is encoded on Chromosome 6 and is typically produced as a 46-kDa homodimer composed of 23-kDa monomers [16, 18]. VEGF is a multifunctional glycoprotein that stimulates endothelial cell mitogenesis.[16,18,19] It serves as a key regulator of both physiological and pathological angiogenesis, playing a role in enhancing vascular permeability.[17,18,20] The g.-2578C>A (rs699947) polymorphism is one of the most functional variants in the VEGF gene, influencing VEGFA expression and being associated with several cardiovascular diseases.[16,21]

N-acetylation, catalyzed by N-acetyltransferase (NAT2), is a critical metabolic process for specific chemicals. In humans, two functional isoforms of NAT exist: NAT1 and NAT2.[22] The NAT2 gene plays an essential role in the human physiological response to various xenobiotic substances, including numerous drugs used to treat hypertension, as well as a wide range of exogenous chemicals present in the environment and dietary sources.[4] NAT2 is an intron-less gene located between 170 and 360 kb on chromosome 8p22, near CpG island clusters. It has a coding region of 873 base pairs, which encodes a protein consisting of 290 amino acids.[4,14] A pharmacogenetic study revealed that such variability was caused by changes in individual NAT2 genotypes, resulting in phenotypic variations in N-acetylation metabolic capacity (ie, rapid or poor acetylation status), which in turn influenced the individual's treatment response.[4,22]

The aldosterone receptor, also known as the mineralocorticoid receptor (MR) or NR3C2, is a member of the nuclear receptor superfamily.[23] It is expressed in various epithelial tissues, including the kidneys, salivary glands, sweat glands, and intestines, where it plays a critical role in enhancing sodium reabsorption and potassium excretion, thus contributing to the regulation of electrolyte balance and blood pressure.[24,25] Encoded by the NR3C2 gene, the mineralocorticoid receptor (MR) is located on the q31.1 region of chromosome 4. This gene spans approximately 400 kb and consists of 9 exons, with exons 2 through 9 encoding the 984-amino acid protein.[26] Mutations in the NR3C2 gene are implicated in various disease states. For example, polymorphisms such as c.-2-358C>G (rs2070950) and c.538G>A (rs5522) have been shown to influence stress sensitivity, reduce cortisol induction, and modify blood pressure regulation and heart failure responses.[27–29]

PKC is a family of enzymes comprising at least 12 distinct isoforms, each contributing to various biological processes, including ion channel regulation, secretion and exocytosis, transcriptional control, and cellular proliferation, differentiation, and survival.[30–32] Moreover, PKC plays a pivotal role in multiple signaling pathways that regulate vascular blood pressure.[32,33] The rs16960228 variant in the PRKCA gene, which encodes PKCα, a major PKC isoform expressed in endothelial cells,[33] has recently been implicated in modulating responses to antihypertensive drugs, as reported in a genome-wide association study (GWAS) of individuals with hypertension.[12,34] Furthermore, expression studies have demonstrated that the rs16960228 variant significantly influences PRKCA expression levels.[12]

Due to the multifactorial nature of hypertension and the intricate physiological-regulating systems that govern its severity and management,[35,36] it is crucial to investigate polymorphisms that are directly or indirectly involved in pathways related to blood pressure regulation and the antihypertensive effect of pharmacological drugs.[37,38] Despite growing evidence supporting the role of gene-environment interactions in hypertension, few studies have examined how specific polymorphisms behave within distinct Middle Eastern populations, which are often underrepresented in global genomic research.

The Jordanian Arab population, in particular, has a unique genetic structure shaped by consanguinity patterns and regional admixture, which may influence allele frequencies and gene-disease associations differently than in other populations. However, comprehensive studies investigating hypertension-related genetic variants within this population remain scarce, limiting the ability to generalize findings from different ethnic groups or to develop population-specific risk assessments and therapeutic approaches. Therefore, this study aims to investigate the association between polymorphisms in the genes VEGFA, NAT2, TANC2, NR3C2, PROX1, PTGER3, and PRKCA and susceptibility to hypertension in the Jordanian Arab population, based on the hypothesis that population-specific genetic variants may contribute to inter-individual differences in hypertension risk.

Materials and Methods

Study Design

The Cardiac Clinic and Coronary Care Department at King Abdullah University Hospital (KAUH) in Irbid, Jordan, served as the recruitment sites for this study, enrolling 224 healthy controls and 200 patients with hypertension from the Jordanian Arab community. These individuals had high blood pressure and were using antihypertensive drugs from different classes. All study participants were 35 years or older and had been on antihypertensive medication for at least one year. The Human Ethics Committee of Jordan University of Science and Technology and King Abdullah University Hospital (KAUH) in Irbid, Jordan, approved the study protocol. Demographic and clinical data were collected from KAUH's electronic medical records system. Informed consent was obtained from all participants.

The study included unrelated Jordanian hypertensive patients who met specific inclusion criteria, including a confirmed clinical diagnosis of hypertension, a minimum age of 35 years, and the availability of medical data in the KAUH registry system. Participants were selected based on eligibility criteria and convenience sampling without randomization. Participants were excluded if they declined to provide written informed consent, had incomplete clinical records, were biologically related to other enrolled participants up to the second degree of kinship, or were not receiving prescribed antihypertensive medications.

Control group participants were classified as healthy based on the absence of clinical diagnoses of hypertension and other common comorbidities, such as diabetes mellitus, renal impairment, cardiovascular disease, or chronic inflammatory conditions. Only individuals with no known history of chronic illness and not receiving antihypertensive or related medications were included as healthy controls. Medical histories were collected through structured interviews and verified, when possible, through the review of available medical records to ensure accurate classification.

A semi-structured interview was used to collect demographic and clinical data from 200 patients. The data included age, gender, weight, lifestyle characteristics (smoking status, ex-smoker, diet, and exercise level), comorbidities (diabetes mellitus, ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular accident, chronic kidney disease, dialysis, atrial fibrillation), the dose of the antihypertensive medications prescribed to patients, antihypertensive drugs types, and different laboratory tests (CBC and chemistry and lipid profile). For privacy and security, each participant was identified by a code rather than their patient name.

According to the World Health Organization (WHO), 1.3 million Jordanians aged 30 to 79 have hypertension out of a total population of 10,699,000 (https://www.who.int/publications/m/item/hypertension-jor-2023-country-profile). The sample size required for this study was calculated using OpenEpi software (version 3.01), assuming a 95% confidence interval (CI), a design effect of 1, a margin of error of 5%, and a hypertension prevalence of 12%. The calculated required sample size was 163, but 200 patients were included in our study, exceeding the minimum required number of participants.

Sample Collection and DNA Extraction

Peripheral blood samples (5 mL) were collected from each participant via venipuncture into sterile EDTA-coated vacutainer tubes to prevent coagulation. Samples were labeled with unique identifiers and processed within 2 hours of collection to minimize DNA degradation. Tubes were stored at 4 °C, and DNA extraction was completed within 24 hours.

Genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. DNA concentration and purity were assessed with a NanoDrop spectrophotometer, with acceptable purity defined as an A260/A280 ratio between 1.8 and 2.0. Samples with lower purity ratios were re-extracted to meet quality standards. DNA integrity was further evaluated by 1% agarose gel electrophoresis to confirm the absence of degradation.

Sample Quality Assessment

Only DNA samples with concentrations ≥20 ng/μL, total yield ≥1 μg, and purity within the specified range were included in the downstream genotyping analysis. Samples failing to meet these criteria were excluded or reprocessed. Over 95% of DNA samples satisfied the predefined quality criteria for concentration and purity required for analysis.

Genotyping Protocol Using Sequenom MassARRAY® System

Genotyping of selected SNPs was performed at the Australian Genome Research Facility (AGRF; Melbourne Node, Melbourne, Australia) using the high-throughput Sequenom MassARRAY® system (iPLEX GOLD, Agena Bioscience, San Diego, CA, USA). This platform combines multiplex PCR, single-base primer extension, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry for accurate and cost-effective SNP genotyping. Initially, multiplex PCR was used to amplify target regions containing the SNPs of interest, generating short PCR products. Residual dNTPs were enzymatically removed using shrimp alkaline phosphatase (SAP). Subsequently, the MassEXTEND® primer extension reaction produced allele-specific DNA fragments, which were analyzed by MALDI-TOF mass spectrometry. Time-of-flight data were processed using SpectroTYPER-RT software to generate genotype calls, ensuring accurate and precise discrimination of SNPs.

Assay Design and Quality Control

Assays were designed based on SNP sequences obtained from the NCBI database, with PCR and single-base extension primers created using MassARRAY software version 3.1. Primer specificity was validated via BLAST searches to avoid off-target amplification. The system supports multiplexing of up to 40 SNPs per run using 384-well plates with automated barcode tracking, enabling high-throughput genotyping. Quality control included the use of positive and negative controls, with genotyping call rates consistently exceeding 95% across samples.

Statistical Analysis

The genotype-phenotype association was statistically analyzed using Pearson's chi-square test (χ^2) and one-way analysis of variance (ANOVA). The odds ratio (OR) with 95% confidence intervals (CI) was calculated using the Statistical Package for Social Sciences (SPSS, version 26.0, SPSS Inc., Chicago, IL). Furthermore, SNPstat was used to evaluate alternative inheritance models, assess Hardy-Weinberg equilibrium (HWE), estimate haplotype frequencies, and investigate the association between haplotypes and disease status (https://www.snpstats.net/start.htm). P-values less than 0.05 were considered statistically significant. The required number of SNPs to account for multiple testing was calculated using the approach described in.[39] The Bonferroni adjustment was applied to adjust the significance level to the threshold α/n, where $\alpha = 0.05$, and "n" represents the number of individual tests.[40]

Results

Population Characteristics and Hardy-Weinberg Test

This study included 224 healthy controls with a mean age of 34.50 years ± 12.44, of whom 61.3% were male. In comparison, the 200 hypertension (HTN) patients had a mean age of 58.84 years ± 10.39, with 57.5% being male. Both the control group and the hypertension patients had their body mass index (BMI) measured, with values of 30.56 ± 5.62 and 33.35 ± 2.25, respectively. The observed genotype distribution was consistent with the Hardy-Weinberg equilibrium ($p > 0.05$), as shown in Table 1.

Table 1 The Genes, Their SNPs, Their Minor Allele Frequencies, and HWE p-value in Cases and Controls

Gene	SNP _ID	Cases (n= 200)			Controls (n =224)		
		MAF	MA	HWE *p-value*	MAF	MA	HWE p-value
NAT2	rs1801280	0.41	C	0.19	0.37	C	0.74
	rs1041983	0.35	T	0.53	0.41	T	0.21
	rs1799929	0.40	T	0.45	0.37	T	0.40
VEGFA	rs699947	0.38	A	0.55	0.48	A	0.09
NR3C2	rs5522	0.05	G	0.43	0.08	G	0.61
TANC2	rs2429427	0.25	A	0.71	0.19	A	0.11

(*Continued*)

Table 1 (Continued).

Gene	SNP _ID	Cases (n= 200)			Controls (n =224)		
		MAF	MA	HWE *p-value*	MAF	MA	HWE p-value
PROX1	rs340874	0.47	C	0.001	0.43	C	0.004
PTGER3	rs11209716	0.49	T	0.78	0.45	T	0.53
PRKCA	rs16960228	0.11	A	1	0.08	A	1
	rs4791040	0.13	C	0.74	0.11	C	0.70
TLE1	rs2378479	0.19	G	0.11	0.18	G	0.79

Abbreviations: MA, Minor allele; MAF, Minor allele frequency; HWE, Hardy-Weinberg Equilibrium.

Allele Frequencies, Genotype Distributions, and Genetic Model Analysis

The distributions of genotypes and alleles are presented in Table 2, and the genotype models for the investigated polymorphisms are outlined in Table 3. The rs699947 polymorphism of VEGFA and the rs2429427 polymorphism

Table 2 Genotype and Alleles Distributions of SNPs Within Genes in HTN Patients and Control

Gene	SNP_ID	Genotype	Frequency		p-value
			N (%) Controls	Cases N (%)	
NAT2	rs1801280	T/T	66 (39%)	63 (32%)	0.34
		C/T	81 (48%)	105 (53%)	
		C/C	21 (13%)	29 (15%)	
		T	213 (63%)	231 (59%)	0.18
		C	123 (37%)	163 (41%)	
	rs1041983	C/C	62 (37%)	82 (42%)	0.05
		C/T	74 (44%)	94 (48%)	
		T/T	33 (20%)	21 (11%)	
		C	198 (59%)	258 (65%)	0.05
		T	140 (41%)	136 (35%)	
	rs1799929	C/C	59 (38%)	67 (35%)	0.72
		C/T	79 (50%)	99 (51%)	
		T/T	19 (12%)	28 (14%)	
		C	197 (63%)	233 (60%)	0.46
		T	117 (37%)	155 (40%)	
VEGFA	rs699947	A/A	44 (26%)	26 (13%)	0.006
		C/A	73 (43%)	97 (49%)	
		C/C	51 (30%)	74 (38%)	
		A	161 (48%)	149 (38%)	0.005
		C	175 (52%)	245 (62%)	
NR3C2	rs5522	A/A	141 (83%)	177 (90%)	0.07
		A/G	28 (17%)	19 (10%)	
		G/G	0 (0%)	1 (1%)	
		A	310 (92%)	373 (95%)	0.11
		G	28 (8%)	21 (5%)	
TANC2	rs2429427	G/G	104 (68%)	108 (55%)	0.04
		G/A	41 (27%)	77 (39%)	
		A/A	9 (6%)	11 (6%)	
		G	249 (81%)	293 (75%)	0.05
		A	59 (19%)	99 (25%)	

(*Continued*)

https://doi.org/10.2147/VHRM.S536434

Table 2 (Continued).

Gene	SNP_ID	Genotype	Frequency		p-value
			N (%) Controls	Cases N (%)	
PROX1	rs340874	C/C	40 (24%)	54 (27%)	0.61
		C/T	64 (38%)	76 (39%)	
		T/T	65 (38%)	67 (34%)	
		C	144 (43%)	184 (47%)	0.26
		T	194 (57%)	210 (53%)	
PTGER3	rs11209716	C/C	53 (32%)	50 (25%)	0.42
		C/T	79 (47%)	101 (51%)	
		T/T	36 (21%)	46 (23%)	
		C	185 (55%)	201 (51%)	0.27
		T	151 (45%)	193 (49%)	
PRKCA	rs16960228	G/G	142 (84%)	154 (78%)	0.35
		G/A	26 (15%)	41 (21%)	
		A/A	1 (1%)	2 (1%)	
		G	310 (92%)	349 (89%)	0.15
		A	28 (8%)	45 (11%)	
	rs4791040	T/T	132 (79%)	148 (76%)	0.73
		C/T	34 (20%)	45 (23%)	
		C/C	1 (1%)	2 (1%)	
		T	298 (89%)	341 (87%)	0.45
		C	36 (11%)	49 (13%)	
TLE1	rs2378479	G/G	6 (4%)	11 (6%)	0.63
		T/G	49 (29%)	54 (27%)	
		T/T	114 (67%)	132 (67%)	
		T	277 (82%)	318 (81%)	0.66
		G	61 (18%)	76 (19%)	

Notes: Significant P values are considered as significant P < 0.05. p-values < 0.004 (0.05/# of SNPs, 0.05/11 = 0.004 after applying multiple comparisons) are considered significant.

Table 3 Genetic Models and Distributions of SNPs Within Genes in HTN Patients and Control

Gene	SNP_ID	Model	Controls N (%)	Cases N (%)	OR (95% CI)	p-value
NAT2	rs1801280	T/T	66 (39.3%)	63 (32%)	1	0.34
		C/T	81 (48.2%)	105 (53.3%)	1.36 (0.87–2.13)	
		C/C	21 (12.5%)	29 (14.7%)	1.45 (0.75–2.80)	
		T/T	66 (39.3%)	63 (32%)	1	0.15
		C/C - C/T	102 (60.7%	134 (68%)	1.38 (0.89–2.12)	
		T/T-C/T	147 (87.5%)	168 (85.3%)	1	0.54
		C/C	21 (12.5%)	29 (14.7%)	1.21 (0.66–2.21)	
		T/T-C/C	87 (51.8%)	92 (46.7%)	1	0.33
		C/T	81 (48.2%)	105 (53.3%)	1.23 (0.81–1.85)	
	rs1041983	C/C	62 (36.7%)	82 (41.6%)	1	0.057
		T/C	74 (43.8%)	94 (47.7%)	0.96 (0.61–1.50)	
		T/T	33 (19.5%)	21 (10.7%)	0.48 (0.25–0.91)	
		C/C	62 (36.7%)	82 (41.6%)	1	0.33
		T/C-T/T	107 (63.3%)	115 (58.4%)	0.81 (0.53–1.24)	

(*Continued*)

Table 3 (Continued).

Gene	SNP_ID	Model	Controls N (%)	Cases N (%)	OR (95% CI)	p-value
		C/C-T/C	136 (80.5%)	176 (89.3%)	1	0.01
		T/T	33 (19.5%)	21 (10.7%)	0.49 (0.27–0.89)	
		C/C-T/T	95 (56.2%)	103 (52.3%)	1	0.45
		T/C	74 (43.8%)	94 (47.7%)	1.17 (0.78–1.77)	
	rs1799929	C/C	59 (37.6%)	67 (34.5%)	1	0.75
		C/T	79 (50.3%)	99 (51%)	1.10 (0.70–1.74)	
		T/T	19 (12.1%)	28 (14.4%)	1.30 (0.66–2.56)	
		C/C	59 (37.6%)	67 (34.5%)	1	0.55
		C/T-T/T	98 (62.4%)	127 (65.5%)	1.14 (0.74–1.77)	
		C/C-C/T	138 (87.9%)	166 (85.6%)	1	0.52
		T/T	19 (12.1%)	28 (14.4%)	1.23 (0.66–2.29)	
		C/C-T/T	78 (49.7%)	95 (49%)	1	0.89
		C/T	79 (50.3%)	99 (51%)	1.03 (0.68–1.57)	
VEGFA	rs699947	C/C	51 (30.4%)	74 (37.6%)	1	0.006
		C/A	73 (43.5%)	97 (49.2%)	0.92 (0.57–1.46)	
		A/A	44 (26.2%)	26 (13.2%)	0.41 (0.22–0.74)	
		C/C	51 (30.4%)	74 (37.6%)	1	0.15
		C/A-A/A	117 (69.6%)	123 (62.4%)	0.72 (0.47–1.12)	
		C/C-C/A	124 (73.8%)	171 (86.8%)	1	0.001
		A/A	44 (26.2%)	26 (13.2%)	0.43 (0.25–0.73)	
		C/C-A/A	95 (56.5%)	100 (50.8%)	1	0.27
		C/A	73 (43.5%)	97 (49.2%)	1.26 (0.83–1.91)	
NR3C2	rs5522	A/A	141 (83.4%)	177 (89.8%)	1	0.08
		A/G	28 (16.6%)	19 (9.6%)	0.54 (0.29–1.01)	
		G/G	0 (0%)	1 (0.5%)	NA (0.00-NA)	
		A/A	141 (83.4%)	177 (89.8%)	1	0.07
		A/G-G/G	28 (16.6%)	20 (10.2%)	0.57 (0.31–1.05)	
		A/A-A/G	169 (100%)	196 (99.5%)	1	0.27
		G/G	0 (0%)	1 (0.5%)	NA (0.00-NA)	
		A/A-G/G	141 (83.4%)	178 (90.4%)	1	0.04
		A/G	28 (16.6%)	19 (9.6%)	0.54 (0.29–1.00)	
TANC2	rs2429427	G/G	104 (67.5%)	108 (55.1%)	1	0.04
		G/A	41 (26.6%)	77 (39.3%)	1.81 (1.14–2.88)	
		A/A	9 (5.8%)	11 (5.6%)	1.18 (0.47–2.96)	
		G/G	104 (67.5%)	108 (55.1%)	1	0.01
		G/A-A/A	50 (32.5%)	88 (44.9%)	1.69 (1.09–2.63)	
		G/G-G/A	145 (94.2%)	185 (94.4%)	1	0.93
		A/A	9 (5.8%)	11 (5.6%)	0.96 (0.39–2.37)	
		G/G-A/A	113 (73.4%)	119 (60.7%)	1	0.01
		G/A	41 (26.6%)	77 (39.3%)	1.78 (1.13–2.82)	
PROX1	rs340874	T/T	65 (38.5%)	67 (34%)	1	0.6
		C/T	64 (37.9%)	76 (38.6%)	1.15 (0.72–1.86)	
		C/C	40 (23.7%)	54 (27.4%)	1.31 (0.77–2.23)	
		T/T	65 (38.5%)	67 (34%)	1	0.38
		C/T-C/C	104 (61.5%)	130 (66%)	1.21 (0.79–1.86)	
		T/T-C/T	129 (76.3%)	143 (72.6%)	1	0.41
		C/C	40 (23.7%)	54 (27.4%)	1.22 (0.76–1.95)	
		T/T-C/C	105 (62.1%)	121 (61.4%)	1	0.89
		C/T	64 (37.9%)	76 (38.6%)	1.03 (0.68–1.57)	

(*Continued*)

https://doi.org/10.2147/VHRM.S536434

Table 3 (Continued).

Gene	SNP_ID	Model	Controls N (%)	Cases N (%)	OR (95% CI)	p-value
PTGER3	rs11209716	C/C	53 (31.6%)	50 (25.4%)	1	0.43
		C/T	79 (47%)	101 (51.3%)	1.36 (0.83–2.20)	
		T/T	36 (21.4%)	46 (23.4%)	1.35 (0.76–2.43)	
		C/C	53 (31.6%)	50 (25.4%)	1	0.19
		C/T-T/T	115 (68.5%)	147 (74.6%)	1.35 (0.86–2.14)	
		C/C-C/T	132 (78.6%)	151 (76.7%)	1	0.66
		T/T	36 (21.4%)	46 (23.4%)	1.12 (0.68–1.83)	
		C/C-T/T	89 (53%)	96 (48.7%)	1	0.42
		C/T	79 (47%)	101 (51.3%)	1.19 (0.78–1.79)	
PRKCA	rs16960228	G/G	142 (84%)	154 (78.2%)	1	0.36
		G/A	26 (15.4%)	41 (20.8%)	1.45 (0.85–2.50)	
		A/A	1 (0.6%)	2 (1%)	1.84 (0.17–20.56)	
		G/G	142 (84%)	154 (78.2%)	1	0.15
		G/A-A/A	27 (16%)	43 (21.8%)	1.47 (0.86–2.50)	
		G/G-G/A	168 (99.4%)	195 (99%)	1	0.65
		A/A	1 (0.6%)	2 (1%)	1.72 (0.16–19.15)	
		G/G-A/A	143 (84.6%)	156 (79.2%)	1	0.18
		G/A	26 (15.4%)	41 (20.8%)	1.45 (0.84–2.48)	
	rs4791040	T/T	132 (79%)	148 (75.9%)	1	0.73
		C/T	34 (20.4%)	45 (23.1%)	1.18 (0.71–1.95)	
		C/C	1 (0.6%)	2 (1%)	1.78 (0.16–19.90)	
		T/T	132 (79%)	148 (75.9%)	1	0.48
		C/T-C/C	35 (21%)	47 (24.1%)	1.20 (0.73–1.97)	
		T/T-C/T	166 (99.4%)	193 (99%)	1	0.65
		C/C	1 (0.6%)	2 (1%)	1.72 (0.15–19.12)	
		T/T-C/C	133 (79.6%)	150 (76.9%)	1	0.53
		C/T	34 (20.4%)	45 (23.1%)	1.17 (0.71–1.94)	
TLE1	rs2378479	T/T	114 (67.5%)	132 (67%)	1	0.63
		G/T	49 (29%)	54 (27.4%)	0.95 (0.60–1.51)	
		G/G	6(3.5%)	11 (5.6%)	1.58 (0.57–4.42)	
		T/T	114 (67.5%)	132 (67%)	1	0.93
		G/T-G/G	55 (32.5%)	65 (33%)	1.02 (0.66–1.58)	
		T/T-G/T	163 (96.5%)	186 (94.4%)	1	0.35
		G/G	6 (3.5%)	11 (5.6%)	1.61 (0.58–4.44)	
		T/T-G/G	120 (71%)	143 (72.6%)	1	0.74
		G/T	49 (29%)	54 (27.4%)	0.92 (0.59–1.46)	

Notes: Significant P values are considered as significant $P < 0.05$. P-values < 0.004 (0.05/# of SNPs, 0.05/11 = 0.004 after applying multiple comparisons) are considered significant.
Abbreviations: OR, Odd ratio; CI, Confidence interval.

of TANC2 (p= 0.0066 and 0.042, respectively) were significantly associated with hypertension. A notable difference in the frequency of the A/A genotype of rs699947 in VEGFA was observed, with 26% in healthy controls compared to 13% in hypertensive patients, suggesting a potential protective role against HTN. The recessive model (A/A vs C/C + C/A) exhibited a significant difference between the studied groups (p = 0.0017, OR = 0.43). The rs2429427 G/G genotype of TANC2 in the dominant model (55% in hypertensive patients compared to 67.5% in healthy controls; p = 0.018, OR = 1.69) and the G/A genotype in the overdominant model (39.3% in hypertensive patients compared to 26.6% in healthy controls; p = 0.012, OR = 1.78) exhibited significant differences in frequency between the hypertensive and control groups. The recessive model of rs1041983 showed a significant difference in the frequency of the T/T genotype (10.7% in HTN patients compared to 19.5% in healthy controls; p = 0.017, OR = 0.49). The

overdominant model of rs5522 revealed a notable difference in the frequency of the A/G genotype (9.6% in HTN patients compared to 16.6% in healthy controls; p = 0.048, OR = 0.54). The remaining polymorphisms studied, including NAT2 rs1799929, rs1801280, PROX1 rs240874, PTGER3 rs11209716, PRKCA rs4791040, and rs16960228, showed no significant differences in the genotype and allele distributions between healthy individuals and those with hypertension in the Jordanian population. The allele frequency analysis reveals no significant association with HTN except for rs699947 VEGFA. The C allele of this variant was significantly associated with the risk of HTN (p= 0.005), with 62% of patients carrying the C allele compared to 52% in healthy controls.

Haplotype Analysis of NAT2 and PRKCA Gene Polymorphisms

The haplotype analysis of the studied SNPs in NAT2 (rs1799929, rs1041983, rs1801280) and PRKCA (rs16960228, rs4791040) revealed no significant association with hypertension in the Jordanian population (p> 0.05). The results of the haplotype analysis are presented in Table 4.

Genotype-Phenotype Correlation Study in Hypertension Patients

As revealed from the clinical genetic association analysis in Supplementary Table S1, Diabetes mellitus (DM) and the number of HTN drugs from all classes were significantly associated with rs699947 of VEGFA (p = 0.006 for both). TANC2 rs2429427 was significantly associated with DM treatment, Angiotensin II Receptor Blockers (ARBs), Anticonvulsants, and other medication for chest pain (angina), and K level (p= 0.03, 0.036, 0.033, 0.009, and 0.034, respectively). PTGER3 rs11209716 was significantly associated with the Number of years of HTN (p= 0.048), number of HTN drugs from all classes (p= 0.037), Left Ventricular Hypertrophy (LVH) (p= 0.013), and other stomach drugs (p= 0.041). In addition to that, PRKCA rs4791040 and rs16960228 exhibited significant association with known and newly diagnosed HTN (p= 0.0041and 0.005), antiplatelet drugs (p= 0.0001 and 0.0004), and other medications (p= 0.008 and 0.017), K (p= 0.0003 and 0.0004), and glucose level (p= 0.04 and 0.084). rs16960228 of PRKCA was associated with angiotensin-converting enzyme inhibitors (ACEi) (p= 0.0011). NAT2 rs1041983 is associated with DBP, ARB drugs, (LVH) Na, and creatinine clearance (p= 0.003, 0.035, 0.013, 0.04, and 0.014). Furthermore, NAT2 rs1799929 and rs1801280 were associated with urea and glucose levels. Finally, rs340874 PROX1 was significantly linked to the number of years of HTN (p= 0.01), exercises (p= 0.015), (ACEi) (p= 0.006), and (LVH) (p= 0.034).

Table 4 Haplotype Analysis of NAT2 Gene Variants Among the HTN Patients and Healthy Controls

Gene	Haplotypes	Frequency		OR (95% CI)	p-value
		Controls	Cases		
NAT2	C C T	0.362	0.398	1	-
	T T C	0.414	0.345	0.75 (0.53–1.05)	0.09
	T C C	0.22	0.241	0.97 (0.66–1.42)	0.86
PRKCA	G T	0.893	0.873	1	-
	A C	0.082	0.114	1.41 (0.85–2.33)	0.19
	G C	0.024	0.012	0.56 (0.18–1.75)	0.32

Notes: Significant *p*-values are considered as significant P < 0.05. p-values < 0.004 (0.05/# of SNPs, 0.05/11 = 0.004 after applying multiple comparisons) are considered significant.
Abbreviations: OR, Odd ratio; CI, Confidence interval.

Discussion

Hypertension (HTN) is the third leading cause of mortality worldwide, contributing to approximately one in eight deaths and accounting for a 13% mortality rate. To the best of our knowledge, few studies have reported statistics on the prevalence of hypertension in Arab countries, and no comprehensive literature reviews have been published to evaluate the prevalence, awareness, or control of hypertension in this region.[41,42] The prevalence of hypertension (HTN) varies considerably, ranging from 16.3% in Jordan (using a blood pressure threshold of 160/95 mmHg) to 44% in Algeria.[41,43] This study investigated the associations of 11 SNPs across 8 genes, including VEGFA (rs699947), NAT2 (rs1799929, rs1041983, rs1801280), NR3C2 (rs5522), TANC2 (rs2429427), PROX1 (rs240874), PTGER3 (rs11209716), TLE1 (rs2378479) and PRKCA (rs4791040 and rs16960228), with BP and hypertension risk in the Jordanian Arab population. Two polymorphisms, rs699947 in VEGFA and rs2429427 in TANC2 (p = 0.006 and 0.042, respectively), showed a significant association with hypertension risk.

Under physiological conditions, VEGF is a crucial angiogenic factor that stimulates the production of endogenous nitric oxide (NO), leading to vasodilation.[19,35,44] VEGF is frequently overexpressed in hypoxic cells.[16] VEGF is induced following ischemic damage and stimulates angiogenesis as a protective strategy for the kidney.[16] Recent studies have shown that lowering blood pressure with angiotensin-converting enzyme inhibitors significantly reduced VEGF expression, whereas increased VEGF expression in glomeruli induced proteinuria, a clinical marker of nephropathy.[16,35] The genetic variations investigated are essential because they alter VEGF expression. Indeed, the AA genotype for rs6999947/g.-2578C>A was associated with lower VEGF expression in peripheral blood mononuclear cells.[19,35,44] The C allele of rs699947 was found to be significantly linked with uncontrolled hypertension. However, there is no documented evidence linking this allele to a reduced response to enalapril in the Brazilian population.[35] The CA and AA genotypes, as well as the dominant and recessive models of the 2578 C > A polymorphism, were found to be protective against HTN susceptibility in the Korean population.[16,21,45] This finding is consistent with our study, which demonstrated that the A/A genotype of rs699947 in VEGFA is a protective factor against hypertension. The recessive model (A/A vs C/C + C/A) showed a significant difference between the studied groups (p = 0.0017, OR = 0.43). In addition, this polymorphism was significantly associated with diabetes mellitus (DM) and the number of HTN drugs from all classes (p= 0.006 for both).

Pharmacogenetics and genomics are becoming increasingly crucial in the postgenomic era, as they enable personalized medicine for individuals.[4] One of the first documented pharmacogenetic characteristics was variation in NAT2 activity.[4] Genetic polymorphisms in the NAT2 locus, which result in either slow or "fast" acetylation phenotypes, have been associated not only with susceptibility to various diseases, including HTN and several types of cancer, but also with differences in therapeutic outcomes when treated with NAT2-metabolized drugs (eg, dapsone, isoniazid, and hydralazine).[4] The NAT2 gene polymorphism has been associated with the development of cirrhotic portal hypertension in research involving the Chinese population, which may serve as a biomarker for genetic predisposition to HTN.[14] However, the recessive model of NAT2 rs1041983 demonstrated a significant association between the T/T genotype and HTN (p= 0.017, OR = 2.03). The allele frequency distribution showed no significant association with HTN in the Jordanian Arab population. Additionally, NAT2 rs1041983 was significantly associated with diastolic blood pressure (DBP), angiotensin II receptor blocker (ARB) medications, left ventricular hypertrophy (LVH), sodium levels, and creatinine clearance (p = 0.003, 0.035, 0.013, 0.04, and 0.014, respectively). Moreover, NAT2 rs1799929 and rs1801280 were associated with urea and glucose levels.

The PRKCA gene regulates various physiological processes, including secretion and exocytosis, the expression of ion channels (such as Ca2+ ion channels), cell growth, and proliferation.[46,47] In a study of Caucasian individuals with hypertension, the intronic SNP rs16960228 in PRKCA was identified as a strong predictor of blood pressure response to hydrochlorothiazide (HCTZ) treatment.[46] The study also found that individuals carrying the rs16960228 A allele exhibited a greater blood pressure response compared to those with the GG genotype.[38,46] Recently, the PRKCA gene SNP rs16960228 was found to be associated with blood pressure responses in hypertensive individuals classified as poor or excellent responders to enalapril.[47] The GA+AA genotype and the A allele were associated with a poorer response to enalapril treatment.[46,47] Previous expression studies have shown that PRKCA expression is significantly higher among GA+AA carriers.[38,46,47] However, prior research on hypertensive patients of European descent found that individuals with the TT genotype who were treated with HCTZ exhibited a smaller reduction in diastolic blood pressure compared to those with the CC or CT genotypes.[38]

In contrast to the current study, no association was found between rs4791040 and rs16960228 genotypes, allele frequencies, and HTN in the Jordanian population. However, these two variants showed significant associations with known and newly diagnosed HTN (p= 0.0041 and 0.005), antiplatelet drugs (p= 0.0001 and 0.0004), and other medications (p= 0.008 and 0.017), K (p= 0.0003 and 0.0004), and glucose level (p= 0.04 and 0.084). Additionally, rs16960228 of PRKCA was associated with angiotensin-converting enzyme inhibitors (ACEi) (p= 0.0011).

The current study has several limitations that should be taken into account when interpreting the findings. First, the relatively small sample size may have reduced statistical power, increased the risk of type II errors, and potentially limited the detection of weaker associations. This underscores the need for larger, well-powered studies to confirm the present findings. Second, as the study was conducted exclusively in a Jordanian cohort, population-specific genetic structure and environmental exposures may have influenced the observed associations, thereby limiting the generalizability of the findings to other ethnic groups. Comparative studies in diverse populations are required to determine whether these associations are broadly applicable or population-specific. Third, while the study explored potential genetic associations, it did not investigate functional mechanisms. Without mechanistic validation, the causal pathways remain speculative, highlighting the importance of integrating genetic, molecular, and clinical data in future research. Finally, the lack of matching for age, sex, and weight between cases and controls represents a limitation. Practical constraints limited our ability to achieve demographic matching, which may introduce potential confounding factors affecting group comparability. We acknowledge that these differences could influence the results; therefore, caution is advised when interpreting the findings. Future studies with larger sample sizes and carefully matched controls are recommended to validate and extend these observations.

Conclusion

Our study identified significant associations of VEGFA rs699947 and TANC2 rs2429427 polymorphisms with hypertension in the Jordanian Arab population. The TANC2 association is novel, while the VEGFA finding corroborates prior evidence, supporting its relevance. These findings improve understanding of hypertension-related genes in blood pressure regulation. They may inform advancements in genetic diagnostics, gene therapy, and personalized treatment, enabling healthcare providers to tailor hypertension management strategies based on patients' genetic profiles for more effective outcomes. However, given the limited number of studies conducted in Arab populations, these results should be interpreted with caution and considered specific to this ethnic group. Further investigations in larger and more diverse populations are needed to confirm the observed associations and evaluate their generalizability.

Abbreviations

HTN, Hypertension; BP, Blood Pressure; VEGF, Human Vascular Endothelial Growth Factor; NAT2, N-acetyltransferase; KAUH, King Abdullah University Hospital; BMI, Body mass index; LVH, Left Ventricle Hypertrophy; OR, Odds Ratios; CI, Confidence interval; MA, Minor allele; MAF, Minor allele frequency; HWE, Weinberg equilibrium; DM, Diabetes mellitus; ACEi, Angiotensin-converting enzyme inhibitors.

Data Sharing Statement

The primary data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board committee at The Jordan University of Science and Technology (No: 4/133/2020). Written informed consent was obtained from all participants before they participated in the study.

Acknowledgments

The authors acknowledge Jordan University of Science and Technology, Jordan, for its administrative and technical support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was funded by the Deanship of Research at Jordan University of Science and Technology, grant number RN: 20200454. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Disclosure

The authors declare that they have no conflicts of interest.

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