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The Norepinephrine Transporter Gene SLC6A2 Variant Is Associated with Essential Hypertension

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Abstract

Introduction: The norepinephrine transporter, encoded by *SLC6A2*, terminates sympathetic signaling. The rs7194256 (C/T) 3'UTR variant has been implicated in altered NET regulation, yet evidence in essential hypertension and Turkish populations is limited.

Methods: We conducted a hospital-based case–control study including 308 adults (153 essential hypertension; 155 normotensive controls). rs7194256 was genotyped by PCR – Restriction fragment length polymorphism analysis. Associations with hypertension (logistic regression) and with clinical/echocardiographic traits (linear regression) were tested under genotype (3-level), dominant (CT+TT vs CC), and additive (per-T-allele) models. Hardy–Weinberg expectations were met in controls and in cases.

Results: Genotype frequencies (CC, CT, and TT) were 54.9%, 38.6%, and 6.5% in cases, and 68.4%, 29.0%, and 2.6% in controls, respectively. Under the dominant model, CT+TT carriers had higher odds of hypertension than CC (adjusted OR 2.00, 95% CI 1.14–3.52). For individual genotypes, adjusted ORs were 1.90 (1.05–3.44) for CT vs CC and 2.86 (0.79–10.33) for TT vs CC. The T allele frequency was 25.8% in cases vs 17.1% in controls, with an adjusted allelic OR=1.84 (1.18–2.85). Systolic blood pressure differed across CC/CT/TT and was higher in CT+TT vs CC. Diastolic blood pressure showed an overall genotype association but was not significant in the dominant model. Arterial stiffness indices and echocardiographic parameters showed no significant associations after adjustment.

Conclusions: In this Turkish population, the SLC6A2 rs7194256 T allele is associated with essential hypertension and relates more strongly to systolic than diastolic phenotypes.

Key words: Norepinephrine plasma membrane transport proteins; polymorphism, genetic; essential hypertension.

Introduction

Systemic arterial hypertension, commonly referred to as hypertension, is defined as a persistent elevation of arterial blood pressure above the normal range. According to etiology, hypertension is classified as either primary (idiopathic, essential) or secondary. Primary hypertension refers to chronically elevated blood pressure without an identifiable underlying cause, whereas secondary hypertension develops due to specific conditions and is more frequently encountered in younger individuals (1). High systolic blood pressure (SBP) is among the leading global risk factors and accounted for ~ 7.8% of total disability-adjusted life years in 2021. This significantly contributes to cardiovascular morbidity and mortality, such as heart failure, myocardial infarction, and stroke, as well as chronic kidney disease (2). It has been estimated that more than one billion people worldwide suffer from hypertension, and its prevalence continues to rise in both developed and developing countries (3). In Turkey, the World Health Organization estimates a 33% prevalence among adults aged 30–79 years (4). These statistics highlight the urgent need to better understand the underlying mechanisms of hypertension in different populations. Blood pressure regulation is maintained through complex interactions between neural and hormonal systems. Norepinephrine (NE), the principal postganglionic neurotransmitter of the sympathetic nervous system, raises arterial pressure via vasoconstriction and cardiac effects, mobilizes glucose (by stimulating glycogenolysis/gluconeogenesis), and—during

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sympathetic activation—contributes to redistribution of blood flow away from the splanchnic bed toward active skeletal muscle (5). The norepinephrine transporter (NET), a sodium- and chloride-dependent monoamine transporter, is responsible for the reuptake of extracellular NE into presynaptic neurons. Approximately 20% of circulating NE is cleared via NET, and more than 90% of NE released at cardiac neuroeffector junctions is recycled by this mechanism (6, 7). Even minor impairments in NE reuptake can therefore result in significant increases in NE spillover into the circulation, leading to sustained sympathetic activation (8). The NET protein is encoded by the *solute carrier family 6 member 2 (SLC6A2)* gene, located on chromosome 16. Comprehensive sequencing of this gene has identified numerous single nucleotide polymorphisms (SNPs). A recently described variant in the 3' untranslated region (3'UTR), rs7194256 (C/T), has been shown to create a novel binding site for microRNA-19a-3p, which may suppress NET translation and reduce NE reuptake (9). This mechanism provides a plausible molecular link between rs7194256 and elevated plasma NE concentrations, which may contribute to the pathogenesis of essential hypertension. Given locus-specific regulation at SLC6A2 and phenotype-dependent sympathetic activation, findings from promoter variants and resistant-hypertension cohorts (10, 11) do not directly inform rs7194256 in essential hypertension. However, data regarding rs7194256 in essential hypertension remain limited, and no studies have investigated this polymorphism in the Turkish population. Based on this background, the present study aimed to evaluate the association between the SLC6A2 rs7194256 polymorphism and essential hypertension in a Turkish cohort. We hypothesized that carriers of the T allele have an increased risk of hypertension and higher blood pressure values compared with CC homozygotes.

Material and methods

Study design and participants: This was a hospital-based case–control study conducted at the Cardiology Clinic of Giresun University Faculty of Medicine Research and Training Hospital. Consecutive adults (≥18 years) with a new diagnosis of essential hypertension were enrolled as cases, and normotensive volunteers without a history of cardiovascular or metabolic disease were enrolled as controls. Secondary hypertension was excluded by clinical evaluation and routine laboratory testing. Patients were ineligible if they had a history of diabetes mellitus, stroke, coronary artery disease, or chronic kidney disease. Controls had no history of hypertension, diabetes mellitus, stroke, ischemic heart disease, or chronic kidney disease.

Clinical, echocardiographic, and laboratory data: Demographic data were recorded at enrollment. Office blood pressure was measured in the seated position with a clinically validated automated oscillometric monitor (HEM-907; Omron Healthcare, Kyoto, Japan) after ≥5 minutes of rest; three consecutive readings were obtained at ~1-minute intervals and averaged. Transthoracic echocardiography was performed according to standard laboratory practice and professional society recommendations using a high-end xMATRIX-capable clinical platform (iE33; Philips Healthcare, Andover, MA, USA), and included left ventricular linear dimensions (end-diastolic and end-systolic diameters, LVEDD and LVESD), wall thicknesses including interventricular septal thickness (IVS) and left ventricular posterior wall thickness (LVPW), left atrial diameter (LAD), left ventricular mass index (LVMI), and left ventricular ejection fraction (LVEF). Routine fasting laboratory tests [fasting plasma glucose (FPG), lipid profile, urea/creatinine, and thyroid-stimulating hormone (TSH)] were analyzed by the hospital laboratory using standardized methods. Variable definitions and units correspond to **Table 1**.

Genotyping of SLC6A2 rs7194256: Peripheral venous blood (5 mL) was collected into EDTA tubes. Genomic DNA was extracted using a commercial kit according to the manufacturer's instructions (Roche Diagnostics, Mannheim, Germany) and stored at −20 °C. We used polymerase chain reaction (PCR) amplification with subsequent restriction fragment analysis (RFLP) to call rs7194256 genotypes. The target region was amplified with primers: Forward 5'-CTCTCTCAAGTGGAGGGGAGA-3' and Reverse 5'-CCCTGGTCCCCTCATAATCC-3', yielding a 386 bp amplicon. The polymorphic site lies within a *BsmI* recognition sequence such that the C allele creates the restriction site, whereas the T allele abolishes it. Following digestion with *BsmI* at 37 °C, the expected fragment patterns were: TT → 386 bp; CT → 386 bp + 295 bp + 91 bp; CC→ 295 bp + 91 bp. Digested products were resolved on 3% agarose gels in 1× TBE, visualized under UV illumination, and genotypes were assigned from the restriction pattern.

Table 1: Demographic, clinical, echocardiographic, and laboratory characteristics of patients with essential hypertension and control subjects

Parameters	Cases n=153	Controls n=155	*p value*
Age (years), (mean ± SD)	52.87 ± 9.37	51.03 ± 8.44	0.058
Gender n (%)			0.430
Female	82 (53.6)	90 (58.1)	
Male	71 (46.4)	65 (41.9)	
BMI (kg/m²)	30.25 ± 4.96	28.27 ± 4.80	0.001*
Office Blood Pressure			
SBP (mmHg)	171.23 ± 16.19	122.83 ± 15.24	<0.001*
DBP (mmHg)	99.32 ± 11.44	74.21 ± 9.98	<0.001*
Arterial Stiffness			
PWV (m/s)	8.03 ± 1.87	7.37 ± 1.17	<0.001*
AIX (%)	23.55 ± 27.30	24.85 ± 16.68	0.054
Echocardiography - Structure			
LVMI (g/m²)	92.67±25.45	67.59±19.67	<0.001*
IVS (cm)	1.04 ± 0.20	0.86 ± 0.14	<0.001*
LVPW (cm)	1.04 ± 0.20	0.87 ± 0.14	<0.001*
LVEDD (cm)	4.73 ± 0.45	4.53 ± 0.51	0.001*
LVESD (cm)	2.67 ± 0.41	2.61 ± 0.39	0.210
Aortic Root Diameter (cm)	3.26 ± 0.25	2.96 ± 0.33	0.005*
Ascending Aorta Diameter (cm)	3.15±0.47	2.95±0.41	<0.001*
LAD (cm)	3.17 ± 0.42	3.00 ± 0.45	0.001*
RVD (cm)	2.44 ± 0.27	2.37 ± 0.30	0.017*
Echocardiography - Function			
LVEF (%)	64.17 ± 3.16	64.81 ± 2.80	0.076
E/Ea	7.88 ± 7.46	5.67 ± 1.61	<0.001*
Laboratory - Core Cardiometabolic			
FPG (mg/dL)	104.89 ± 24.21	99.00 ± 13.24	0.004*
Urea (mg/dL)	30.27 ± 8.16	26.91 ± 7.16	0.001*
Serum Creatinine (mg/dL)	0.81 ± 0.18	0.77 ± 0.16	0.40
TC (mg/dL)	207.52 ± 41.11	200.64 ± 36.47	0.076
TG (mg/dL)	160.21 ± 93.64	149.34 ± 73.82	0.636
HDL-C (mg/dL)	48.48 ± 12.60	49.94 ± 12.23	0.251
LDL-C (mg/dL)	128.35 ± 34.31	121.26 ± 33.29	0.026*
TSH (mIU/L)	2.02 ± 1.85	2.39 ± 5.89	0.691

Data are presented as mean ± standard deviation or n (%). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; AIX, augmentation index; LVMI, left ventricular mass index; IVS, interventricular septal thickness; LVPW, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; RVD, right ventricular diameter; LVEF, left ventricular ejection fraction; E/Ea, ratio of early transmitral inflow velocity to early diastolic mitral annular tissue velocity. FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone.

Ethical Approval: The study protocol was approved by the Giresun University Clinical Research Ethics Committee (Approval No. 12, Date 20.12.2017) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent.

Statistical Analysis: Analyses were conducted with IBM SPSS Statistics. Continuous variables are summarized as mean ± standard deviation or median (interquartile range) as appropriate; categorical variables as n (%). Normality was assessed with Shapiro–Wilk. Group comparisons used independent-samples t-test or Mann–Whitney U-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Genotype and allele distributions were compared by χ^2, with Hardy–Weinberg equilibrium (HWE) tested in cases and controls. Genetic associations with hypertension were evaluated using logistic regression under genotype (3-level), dominant

(CT+TT vs. CC) and additive (per-T-allele) models; results are reported as odds ratios (OR) and 95% confidence intervals (CI). Associations between genotype and continuous traits (e.g., SBP, DBP, echocardiographic and laboratory parameters) were evaluated using multiple linear regression. Unless otherwise specified, multiple models were adjusted for age, sex, body mass index (BMI), fasting plasma glucose (FPG), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, and serum creatinine; all reported p values are adjusted for these covariates, and $p < 0.05$ was considered statistically significant.

Results

Clinical and demographic characteristics: A total of 308 individuals were included in the study, comprising 153 patients with essential hypertension and 155 normotensive controls. Baseline demographic, clinical, echocardiographic, and laboratory characteristics of the study population are presented in Table 1. There was no significant difference between patients and controls with respect to age and sex distribution. BMI was elevated in the patient group relative to controls (30.25 ± 4.96 vs 28.27 ± 4.80 kg/m²; p=0.001).

Table 2: Genotype and allele frequencies of the rs7194256 polymorphism in patients with essential hypertension and control subjects

Genotype	Case (%) n=153	Control (%) n=155	p value	OR (95% CI)	p value	Adjusted OR (%95 CI)	Adjusted p value
rs7194256			0.030*				
CC	84 (54.9)	106 (68.4)		1			
CT	59 (38.6)	45 (29.0)		1.65 (1.02 – 2.68)	0.040	1.90 (1.05-3.44)	0.035*
TT	10 (6.5)	4 (2.6)		3.16 (0.96– 10.42)	0.049	2.86 (0.79-10.33)	0.109
CT+TT	69 (45.1)	49 (31.6)		1.78 (1.11– 2.83)	0.015	2.00 (1.14-3.52)	0.016*
Alleles			0.012*				
C	227 (74.2)	257 (82.9)		1			
T	79 (25.8)	53 (17.1)		1.69 (1.14 – 2.50)	0.008	1.84 (1.18-2.85)	0.012*

Data are expressed as n (%). Odds ratios (OR) and 95% confidence intervals (CI) were calculated. p values are adjusted for age, sex, BMI, fasting plasma glucose, LDL-C, HDL-C, triglycerides, and serum creatinine.

Office blood pressure values were markedly elevated in the hypertensive group (SBP 171.2 ± 16.2 vs. 122.8 ± 15.2 mmHg; DBP 99.3 ± 11.4 vs. 74.2 ± 10.0 mmHg; both $p < 0.001$). Echocardiographic assessment demonstrated significantly higher LVMI, IVS, LVPW, and LAD in patients compared with controls, indicating structural cardiac alterations associated with hypertension. Laboratory evaluation revealed higher FPG, urea, and LDL-cholesterol levels in the hypertensive group (all $p < 0.05$).

Genotype and allele frequencies: The distribution of rs7194256 genotypes and alleles is presented in Table 2. The frequency of the CC genotype was higher in the control group (68.4%) compared with hypertensive patients (54.9%). Carriers of the CT genotype were significantly more prevalent among hypertensive patients (38.6% vs. 29.0%), with an adjusted odds ratio (OR) of 1.90 (95% CI: 1.05–3.44, $p = 0.035$). Although the TT genotype was less frequent overall, it tended to be associated with an increased risk of hypertension (adjusted OR: 2.86, 95% CI: 0.79–10.33, $p = 0.109$). In the dominant model (CT+TT vs. CC), carriers of the T allele had a significantly higher risk of hypertension compared with CC homozygotes (adjusted OR: 2.00, 95% CI: 1.14–3.52, $p = 0.016$). In the allelic analysis, T-allele frequency was higher among patients (25.8%) than controls (17.1%), yielding an adjusted OR=1.84 (95% CI 1.18–2.85; p=0.012). Genotype distributions conformed to Hardy–Weinberg equilibrium in both controls ($\chi^2 = 0.09$, $p = 0.76$; T-allele frequency 0.171) and patients ($\chi^2 = 0.01$, $p = 0.93$; T-allele frequency 0.258). All p values are adjusted.

Genotype–phenotype associations: As summarized in Table 3, office SBP differed across genotype groups (CC, CT, TT; overall adjusted $p = 0.028$), and the dominant comparison (CT+TT

Table 3: Association between rs7194256 genotypes and demographic/clinical characteristics in the total study population

	CC (n=190)	CT (n=104)	TT (n=14)	Adjusted p value[a]	CT+TT (n=118)	Adjusted p value[b]
SBP (mmHg)	143.76±28.61	148.46±29.81	158.21±28.21	0.028*	149.62±29.68	0.029*
DBP (mmHg)	85.88±16.03	86.40±16.72	97.21±18.67	0.035*	87.69±17.24	0.096
PWV (m/s)	7.65±1.44	7.71±1.87	8.20±1.25	0.068	7.77±1.81	0.114
AIX (%)	24.21±17.86	23.92±30.19	26.29±10.61	0.112	24.20±28.54	0.382
LVMI (g/m²)	78.62±25.89	80.89±24.97	90.08±32.10	0.296	81.94±25.87	0.067
IVS (cm)	0.93±0.19	0.96±0.19	0.97±0.32	0.322	0.96±0.21	0.130
LVPW (cm)	0.95±0.19	0.97±0.18	1.02±0.24	0.353	0.98±0.19	0.239
LVEDD (cm)	4.62±0.52	4.62±0.46	4.79±0.34	0.182	4.64±0.45	0.152
LVESD (cm)	2.64±0.39	2.66±0.42	2.55±0.45	0.378	2.64±0.43	0.532
Aortic Root Diameter (cm)	3.03±0.37	3.24±0.25	3.32±0.56	0.339	3.25±0.36	0.250
LAD (cm)	3.07±0.46	3.13±0.41	2.93±0.48	0.246	3.11±0.20	0.604
RVD (cm)	2.42±0.30	2.36±0.26	2.55±0.26	0.581	2.38±0.26	0.395
LVEF (%)	64.45±3.07	64.77±2.67	63.33±3.73	0.397	64.60±2.84	0.366
E/Ea	6.23±5.34	7.07±2.78	11.04±13.61	0.125	7.54±5.32	0.128

Data are presented as mean ± standard deviation. All p values are adjusted for age, sex, BMI, fasting plasma glucose, LDL-C, HDL-C, triglycerides, and serum creatinine; two-sided $p < 0.05$ was considered statistically significant. [a] Adjusted p value from multivariable linear regression with indicator terms for CT and TT (reference = CC). [b] Adjusted p value for the dominant genetic model comparison (CT+TT vs CC) from multivariable linear regression. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; AIX, augmentation index; LVMI, left ventricular mass index; IVS, interventricular septal thickness; LVPW, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; RVD, right ventricular diameter; LVEF, left ventricular ejection fraction.

vs CC) was also significant (adjusted $p = 0.029$). For diastolic blood pressure (DBP), the overall genotype effect was significant (overall adjusted $p = 0.035$), whereas the dominant comparison was not (adjusted $p = 0.096$). Pulse wave velocity (PWV) showed a non-significant trend across genotypes (overall adjusted $p = 0.068$) and was non-significant in the dominant model (adjusted $p = 0.114$). Other arterial stiffness indices [e.g., augmentation index (AIX)] and echocardiographic measures (e.g., LVMI, IVS, LVPW, LAD, LVEF) did not differ significantly (all overall and dominant adjusted $p \geq 0.05$).

Discussion

In this case–control study, we found that the rs7194256 variant of the norepinephrine transporter gene, *SLC6A2* was associated with essential hypertension. Specifically, the T allele was more frequent in patients than in controls, and carriers of the T allele (CT+TT) had higher odds of hypertension compared with CC homozygotes under a dominant model. In genotype-specific analyses, both CT and TT genotypes showed higher odds of hypertension relative to CC. However, only the comparison for CT versus CC reached conventional statistical significance, whereas TT versus CC did not, which is most likely attributable to the very small number of TT homozygotes (10 cases and 4 controls) and the resulting limited statistical power rather than to the absence of an effect. The fact that the odds ratio for TT was numerically higher than for CT, together with the significant per-allele effect and the dominant comparison (CT+TT vs CC), is compatible with a dose–response pattern in which a higher T-allele load confers greater risk, although our sample size does not allow this to be confirmed formally. In the adjusted models, the genotype effect was more consistent for SBP (significant in both the overall and dominant tests) than for DBP (significant in the overall test, but not the dominant test), indicating a stronger link to systolic pressor physiology in this cohort (Table 3). Between-genotype differences for arterial stiffness indices

(PWV and AIX) and echocardiographic measures (e.g., LVMI, IVS, LVPW, LAD, LVEF) were small and not statistically significant; routine biochemical parameters (fasting glucose, lipid profile, renal indices, TSH) were likewise comparable across genotypes (Table 3). Collectively, these findings indicate that rs7194256 is linked primarily to pressor rather than structural phenotypes in our sample. Physiologically, termination of noradrenergic signaling depends on the NET, a Na^+/Cl^--dependent transporter encoded by *SLC6A2*, which rapidly recaptures neuronally released norepinephrine into presynaptic terminals (12). Classic experimental and human studies demonstrate substantial neuronal reuptake in the heart and show that reduced reuptake augments norepinephrine spillover and sustains sympathetic drive (6-8, 13, 14). In NET-deficient mice, wakefulness and activity are accompanied by tachycardia and higher blood pressure, supporting a causal link between reduced NET function and pressor physiology (15). Taken together, these data provide a coherent biological framework for our genetic association. Across SLC6A2 loci and populations, results have been heterogeneous. In young Caucasian men, Zolk et al. (10) linked the promoter variant rs168924 to lower SBP and reduced hypertension prevalence, whereas Ono et al. (16) associated SLC6A2 variation with hypertension in a Japanese cohort. Additional studies in Chinese cohorts reported associations of promoter polymorphisms with essential hypertension (17, 18), while others did not find major effects of SLC6A2 variants on certain adrenergic phenotypes (19). Such variability likely reflects locus-specific regulatory biology (promoter vs. 3'UTR), ancestry and linkage structure, age/sex composition, phenotype definitions (essential vs. resistant hypertension), and environmental context. Importantly, family and twin studies indicate that ~30–50% of blood pressure variance is heritable (1, 20), underscoring the rationale for population-specific genetic studies such as ours. With respect to rs7194256, molecular evidence indicates that the T allele creates a miR-19a-3p binding site in the 3'UTR, leading to post-transcriptional repression of NET and diminished neuronal reuptake (9). Clinically, Eikelis et al. (11) reported that T-allele carriers with resistant hypertension had higher ambulatory SBP and increased arterial NE with a lower 3,4-dihydroxyphenylglycol (DHPG)/NE ratio—consistent with impaired neuronal clearance. Although our cohort comprised essential rather than resistant hypertension, the directionality is concordant: a variant predicted to lower NET activity aligns with greater hypertension risk. While we did not measure catecholamines or NET expression, our findings are compatible with this mechanistic pathway. Strengths of this work include strict case/control definitions (newly diagnosed essential hypertension; exclusion of secondary causes), standardized clinical and echocardiographic phenotyping, and internally controlled genotyping with concordant HWE.

Study Limitations: Limitations include the single-center design and the lack of external replication, which may limit generalizability. Second, we did not obtain ambulatory blood pressure monitoring data; therefore, white-coat effects, nocturnal blood pressure patterns, and short-term variability could not be assessed. Third, no plasma/urinary catecholamine or related biochemical measurements were available, precluding a more direct functional interrogation of the NET pathway and limiting mechanistic inference.

Conclusion

In summary, the SLC6A2 rs7194256 T allele was associated with essential hypertension in this Turkish cohort, and genotype–phenotype analyses point toward preferential involvement of systolic rather than diastolic blood pressure, without detectable differences in arterial stiffness or cardiac structure. These findings align with prior evidence that reduced NET-mediated reuptake amplifies sympathetic signaling and elevates blood pressure. Replication in larger, multi-center Turkish cohorts, integration of 24-hour ambulatory blood pressure and catecholamine/DHPG data, and functional assays will be important next steps to clarify causality and clinical relevance.

Ethical approval: Ethics Committee permission was obtained from Giresun University Medical Faculty Clinical Research Ethics Committee with the decision number 12 on 20.12.2017.

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