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Relationship Between GRK4 Polymorphisms And Essential Hypertension. A Study In A Group Of Turkish Subjects

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Abstract

Background/Purpose: G protein-coupled receptor kinase (GRK4) is associated with essential hypertension (EHT). GRK4 regulates sodium balance in the proximal tubules of the kidney. In this study, the possible roles of A142V and A486V polymorphisms in the development of hypertension were investigated in a Turkish population.

Methods: Genomic DNA was obtained from white blood cells using the standard DNA isolation kit (Roche). Genotypes of variants of GRK4 were determined by Polymerase chain reaction (PCR) - Restriction fragment length polymorphism (RFLP) analysis.

Results: In this study, GRKA142V and A486V polymorphisms were found to be associated with EHT in the Turkish population ($P<0.05$). The relationship between EHT and the A142V polymorphism was found to be more significant in men than in women.

Conclusion: Our results show that A142V and A486V polymorphisms of the GRK4 were associated with EHT in a Turkish population. As far as we know, this is the first study on the association between the GRK4 A142V and A486V gene polymorphisms and essential hypertension in the Turkish population. GRK4 could be a new therapeutic target for hypertension.

Keywords: Genetic Polymorphism, G-Protein-Coupled Receptor Kinase 4, Signal Transduction Pathways

Özet

Amaç: G protein kenetli reseptör kinaz (GRK4) esansiyel hipertansiyon (EHT) ile ilişkilidir. GRK4 böbreğin proksimal tübüllerinde sodyum dengesini düzenlemektedir. Bu çalışmada A142V ve A486V polimorfizmlerinin hipertansiyon gelişimindeki olası rolleri Türk bireylerde araştırılmıştır.

Yöntemler: Genomik DNA, standart kit (Roche) kullanılarak beyaz kan hücrelerinden elde edilmiştir. GRK4'ün varyantlarının genotipleri Polimeraz zincir reaksiyonu (PZR) – Restiriksiyon fragment uzunluk polimorfizmi (RFLP) analizi ile belirlenmiştir.

Bulgular: Bu çalışmada Türk bireylerde A142V ve A486V polimorfizmlerinin EHT ile ilişkili olduğu bulunmuştur. EHT ile A142V polimorfizminin ilişkisi kadınlara göre erkeklerde daha anlamlı bulunmuştur.

Sonuç: Sonuçlarımız, Türk popülasyonunda GRK4'ün A142V ve A486V polimorfizmlerinin EHT ile ilişkili olduğunu göstermektedir. Bilgilerimiz ışığında bu çalışma, Türk toplumunda GRK4 A142V ve A486V gen polimorfizmleri ile esansiyel hipertansiyon arasındaki ilişkiyi inceleyen ilk çalışmadır. GRK4 hipertansiyon için yeni bir tedavi hedefi olabilir.

Anahtar Kelimeler: Genetic Polimorfizm, G-Protein-Kenetli Reseptör Kinaz 4, Sinyal ileti yolları

Introduction

Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or higher, a diastolic blood pressure (DBP) of 90 mmHg or higher, or the use of antihypertensive medication (1).

Hypertension is among the most common chronic medical conditions characterized by a persistent rise in arterial pressure. Essential hypertension is considered to be a typical complex disease and is influenced by both genetic and environmental factors (2). Dopamine is important in the regulation of sodium balance and blood pressure via renal mechanisms (3). The D1-like receptors, comprising the D1 and D5 receptor subtypes, couple to the stimulatory G proteins Gs and Golf and activate adenylyl cyclases (4-6). In the case of sodium excess, locally produced dopamine acts on renal tubule cells to prevent sodium reabsorption (7). Dopamine exerts its natriuretic effects by acting on D1-like and D2-like receptors in the renal proximal tubule (7, 8). Irregularities in dopamine receptor function in the renal proximal tubules have been reported in genetic hypertension (8,9). The increase in dietary sodium stimulates renal dopamine production, which is impaired in some hypertensive patients. The D2-like receptors, comprising the D2, D3, and D4 GPCR kinases (GRKs) belong to a 7- member family of serine/threonine protein kinases and are involved in the desensitization of G protein-coupled receptors including the D1 receptor (7,9). GRKs 1 and 7 belong to the rhodopsin family; GRKs 2 and 3 belong to the β-adrenergic receptor kinase family, and GRKs 4, 5, and 6 belong to the GRK4 family (9).

It has been reported that the expression of GRK4 is significantly increased after myocardial infarction (10,11). The GRK4 Loci on human chromosome 4 have been linked to essential hypertension. The GRK4 locus at 4p16.3 has been linked to the increase in blood pressure from childhood to adulthood and to hypertension in adults (3,12). GRK4 gene variants (R65L, A142V and A486V) are reported to be associated with salt-sensitive or salt-resistant essential hypertension (13). Three variants of the isoform of GRK4γ, R65L, A142V, and A486V have been reported to increase GRK activity, but the mechanism has not yet been elucidated. Constitutive activation of GRK4 γ gene variants causes D1R phosphorylation or modification in the renal proximal tubule. The uncoupling of the D1R from its G protein– effector complex decreases D1R function and impairs its ability to decrease sodium transport (9). Different studies show that GRK4 is a risk factor for hypertension because of its negative regulation of the renal dopaminergic system (14).

The aim of this study was to investigate the association between the GRK4 A142V and A486V gene polymorphisms and essential hypertension in a group of Turkish subjects.

Methods

All reagents for PCR amplification and gel electrophoresis were purchased from MBI- Fermentase Life Sciences. All other chemicals were obtained from Sigma (Darmsladt, Germany), unless stated otherwise.

Collection of samples

Approval required for the study was obtained from the Ethics Committee of Marmara University School of Medicine. The control group consisted of healthy individuals with no history of hypertension and no evidence of any metabolic disorders. Hypertension samples were collected from patients with essential hypertension who applied to Dr. Sadi Konuk Training and Research Hospital Cardiology and Internal Diseases Polyclinic and Marmara University Hospital Hypertension Clinic. Information about gender, age, weight, height, SBP, DBP, family history and medical history of the patients and whether they used drugs for treatment were obtained from the patients. The control group consisted of 105 individuals with SBP lower than 140 mmHg, DBP lower than 90 mmHg, who were not hypertensive, and did not use antihypertensive drugs. Patients with hypertension consisted of 95 individuals with blood pressure above these values and on antihypertensive treatment. Individuals with alcohol dependence, heart disease or hormone replacement therapy, diabetes or kidney disease were excluded from the study. The criteria to be followed in patient selection are specified in the Ethics Committee Follow-up Form.

DNA Isolation

Peripheral venous blood was collected into EDTA-coated tubes. Genomic DNA was extracted using DNA isolation kit cat no.11 667 327001 (Roche Diagnostic, USA). DNA purity and quantitation were assessed by A260/280 ratios.

Genotyping

DNA samples were amplified by Polymerase chain reaction (PCR) with the appropriate primers for A142V, A486V polymorphisms as shown in Table 1.

TABLE 1: Primers and restriction endonucleases		
Polymorphisms	**Primer sequence**	**Restriction endonucleasese (RT)**
A142V,679CT	5′-GCAGAAGGTTGGGTGGTGT-3′_ (forward)	BSURI (HaeIII), (37°C)
	5′-AGGAGGAGAACCCTTCCAAAAAGG3′-(reverse)	
A486V,1711CT	5′-AGAGTGGCGGTGTTTATGCG-3′_ (forward)	
	5′-GGTGTCCAGGTAGATCCCTTTCAGC3′-(reverse)	AciI (SsiI), (37°C)

Amplification reactions were carried out on DNA Thermal Cycler (Thermo Electron) in a 50 µl-volume containing 1.5 µg of genomic DNA, 1 U Taq DNA polymerase enzyme, 2 pmol of each primer, 0.2 mmol/L of each dNTP, 10X PCR buffer provided by the manufacturer (Fermentase) and $MgCl_2$ at 1.5–4.0 mM. The primers used are based on previously published sequences (15). For A142V, polymerase chain reaction began with a denaturation step at 94°C for 5 min, followed by 28 cycles of denaturation at 94°C (15 sec), annealing at 58°C (15 sec), and extension at 72°C (30 sec). This was followed by a final extension step at 72°C for 2-7 min. The cycle parameters for A486V were as follows: 5 min of denaturation at 94°C, followed by 15 sec at 94°C, 15 sec at 55°C, 30 sec at 72°C for 38 cycles, and a final extension step of 2-7 min at 72°C.

DNA samples amplified by polymerase chain reaction were run on 2% agarose gels at 80-100 volts (50 mA) for 30 minutes. The gels were stained with EtBr and examined under UV.

To examine the A142V polymorphism, 201 bp (base pair) PCR products were treated with 1 unit of BSURI (HaeIII) enzyme (MBI-Fermentase) at 37ºC for 16 hours. After the enzyme was inactivated at 80ºC, enzyme cleavage was checked with 3% agarose gel electrophoresis. Two bands of 176 and 25 bp were observed for the CC allele, a single band of 201 bp for the TT allele, and three bands of 201, 176 and 25 bp for the CT allele. To examine the A486V polymorphism, 187 bp PCR products were reacted with 1 unit enzyme AciI (SsiI) (MBI- Fermentase) at 37ºC for 15 minutes. After the enzyme was inactivated at 65°C, enzyme cleavage was checked with 3% agarose gel electrophoresis. Three bands of 113, 49, and 25 bp were observed for the CC allele, two bands of 138 and 49 bp for the TT allele, and four bands of 138, 113, 49, and 25 bp for the CT allele. For samples considered to have a single nucleotide polymorphism, PCR was carried out in 50 µl volume. The results were confirmed by sequencing. The PCR products were cleaned with the nucleospin PCR cleaning kit in 25 µl volume with a concentration of at least 50 ng/µl.

Sequencing

Polymerase chain reaction products were purified with a High Pure PCR purification Kit cat no. 1796 828 (Roche Diagnostics, Mannheim, Germany) and sequenced with a dye terminator sequencing kit on the Applied Biosystems ABI automated DNA sequencer (Iontek, Istanbul, Turkey).

Statistical Analysis

Unpaired t-test statistical analysis was performed on patient-control groups. Hardy-Weinberg equilibrium was determined for each polymorphism with the $\chi 2$ test, and a comparison was made between the allelic frequency distribution and phenotypes of the polymorphisms.

Results

The characteristics of the EHT patients and normotensive controls are shown in Table 2

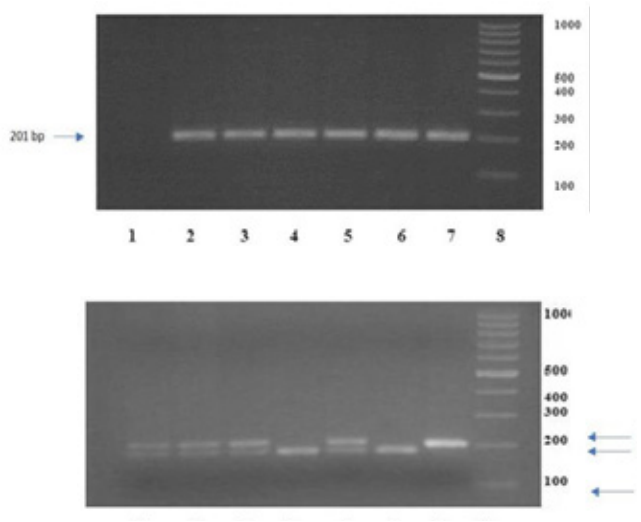
TABLE 2: Demographic and clinical data of healthy controls (NT) and essential hypertensive patients (EHT).			
Parameters	**NT**	**EHT Patients**	**P**
Number of individuals	105	95	-
Male	62	35	-
Female	43	60	-
Age	35.50±2.009	58.86±1.290	<0,0001*
BMI kg/m2	22.02±0.5323	29.52±0.4934	<0,0001*
SBP mmHg	116.3±1.492	152.2±1.884	<0,0001*
DBP mmHg	74.30±1.116	92.65±1.220	<0,0001*

*P<0.0001 Compared with the control group Abbreviations: BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure.

Detection of A142V Polymorphism by BSURI (HaeIII) Restriction Enzyme

PCR products were digested with BSURI (HaeIII) restriction enzyme. The reaction mixtures were run on 3% agarose gels and gels were stained with ethidium bromide. The representative restriction fragment digests are shown in Fig 1.

FIGURE 1

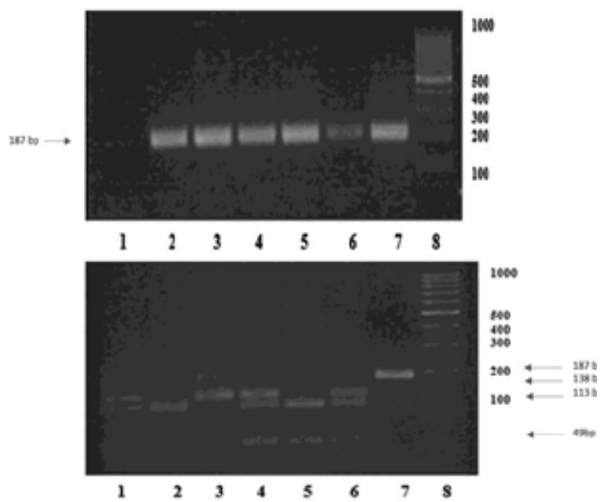


Genotyping for A142V polymorphism of GRK4 using PCR-RFLP. a) PCR products for the A142V polymorphism, 201 bp. b) GRK4-specific PCR products were digested with the BSURI restriction enzyme. Two bands of 176 and 25 bp are seen for the CC allele, three bands of 201, 176 and 25 bp for CT, and a single band of 201 bp for TT.

Detection of A486V Polymorphism by AciI (SsiI) Restriction Enzyme

PCR products were digested with AciI (SsiI) restriction enzyme. The reaction mixtures were run on 3% agarose gels and gels were stained with ethidium bromide. The representative restriction fragment digests are shown in Fig 2.

FIGURE 2



Genotyping for A486V polymorphism of GRK4 using PCR-RFLP. a)PCR products for the A486V polymorphism,187 bp . b) GRK4-specific PCR products were digested with the AciI restriction enzyme. Three bands of 113, 49, and 25 bp are seen for the CC allele, two bands of 138 and 49 bp for the TT allele, and four bands of 138, 113, 49, and 25 bp for the CT allele.

All genotype distributions are in Hardy-Weinberg equilibrium. Genotypes and allele frequencies for polymorphisms A142V and A486V of the GRK4 gene are shown in Table 3.

For A142V, among 105 individuals in the control group, the CC allele was found in 47, the TT allele in 5, and the CT allele in 53 individuals; of the 95 individuals examined in the patient group, the CC allele was found in 42, the TT allele in 21, and the CT allele in 29 individuals. The T allele was calculated as 63% in the control group and 71% in the patient group. When the TT allele frequency was compared in the control and patient groups, the difference was found to be statistically significant. When the T allele (CT/2+TT) was calculated separately, the difference was also found to be statistically significant.

For A486V, among 71 individuals in the control group, the CC allele was found in 31, the TT allele in 2, and the CT allele in 38 individuals; of the 72 individuals examined in the patient group, the CC allele was found in 28, the TT allele in 13, and the CT allele in 31 individuals.

The T allele was calculated as 42% in the control group and 57% in the patient group. When the TT allele frequency was compared in the control and patient groups, the difference was found to be statistically significant when the difference was calculated separately. When the Tallele (CT/2+TT) was calculated separately, the difference was also found to be statistically significant.

When the control and patient groups were compared, the difference between the A142V and A486V polymorphism was found to be statistically significant. For the A486V polymorphism, the difference was found to be significant when we performed statistical analysis by taking the number of samples by 3 times.

Discussion

In this study, the relationship between GRK4 gene A142V and A486V polymorphisms and EHT was investigated in a Turkish population. In our study, the frequency of the T allele of the A142V polymorphism was found to be 30% in the control group and 38.5 % in the patient group. Our results suggested that A142V polymorphism is associated with essential hypertension. The frequency of the T allele for A486V was found to be 29.5 % in the control group and 39.5% in the patient group. Statistical analysis indicated that this polymorphism may also be associated with essential hypertension. There is increasing evidence that G protein-coupled receptor kinase 4 plays an important role in HT, especially in salt-sensitive HT. Different researchers have found that the expression of the A142V variant of GRK4γ in transgenic mice causes HT by disrupting the natriuretic effect of the D1 receptor (7,16). These findings suggest that constitutively active GRK4γ variants contribute to hypertension because the downstream

TABLE 3: Genotypes and allele frequencies polymorphisms A142V and A486V of GRK4 gene in a Turkish population.

Genotypes	NT (n=105) n (%)	EHT (n=95) n (%)	P
A142V			0.0003
CC	47 (44.7)	42 (44,2)	
CT	53 (50.4)	29 (30.5)	
TT	5 (4.7)	21 (22.1)	
*P<0.0001 Compared with the control group Abbreviations: BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure.			
Genotypes	**NT (n=71) n (%)**	**EHT (n=72) n (%)**	**P**
A486V			0.0115
CC	31 (43.6)	28 (38.8)	
CT	38 (53.5)	31 (43)	
TT	2 (2.8)	13 (18)	
Allele frequencies			**P**
A142V			0.0880
T	63 (30)	71 (38.5)	
C	147 (70)	113 (61.4)	
A486V			0.0827
T	42 (29.5)	57 (39.5)	
C	100 (70.4)	87 (60.5)	

Distributions of A142V and A486V genotype and allele frequencies in the NT and EHT group classified according to gender are shown in Table 4.

TABLE 4: Genotypes and allele frequencies in a Turkish Population according to gender

Genotypes	NT Female (%)	EHT Patient Female n (%)	Pb (1x/3x) *	NT Male n (%)	EHT Patient Female n (%)	Pb (1x/3x) *
A142V						
CC	18 (41.8)	33 (55)	0.0941/<0.0008	29 (46.7)	10 (27)	0.0001/<0.0001
CT	21(48.8)	17 (28.3)		32 (51.6)	16 (43.2)	
TT	4 (9.3)	10 (16.6)		1 (1.6)	11 (29.7)	
A486V						
CC	14 (45.1)	21 (43.7)	0.0465/0.0001	17 (42.5)	7 (29.1)	0.1245/0.0019
CT	17 (54.8)	19 (39.5)		21 (52.5)	12 (50)	
TT	0 (0)	8 (16.6)		2 (5)	5 (20.8)	
Allele frequencies						
A142V						
T	29	37	0.7622/0.4846	34	38	0.0012/<0.0001
A486V						
T	17	35	0.2986/0.0454	25	22	0.0392/0.0003

effectors of the D1 receptor and active GRK4γ variants do not combine with the downstream effectors of the D1 receptor, thus impairing the natriuretic effect of dopamine. This has the final outcome of reducing sodium excretion by the kidneys and further development of hypertension (7,16). Different investigators have shown that GRK4 affects hypertension by GPCR-mediated regulation of renal and arterial function. Studies demonstrate that GRK4 gene variants (R65L, A142V, and A486V) are related to salt-sensitive or salt-resistant essential hypertension (11,13). Researchers show that GRK4 expression and activity are higher in the hypertensives (12). These studies also suggest that among patients with essential HT, there is a reduced response of the D1 receptor in the proximal tubules as a result of dissociation of the D1 receptor from the G protein/effector enzyme complex (12,16). Williams et al. (17) in their study on Ghanaians found that there was no statistical difference between normotensive and hypertensive individuals, but that SBP was low in homozygous carriers of the A486V allele. Wang et al. (15) in their study in northern China showed that the A486V polymorphism was associated with HT and the A allele of the A486V polymorphism was associated with HT. Speirs et al. (7) found that the V allele of the A486V polymorphism was associated with higher SBP and HT in white British Australians. The same group of investigators also determined that the R65L and A142V polymorphisms were not significantly associated with HT. They found that the L allele of the R65L polymorphism and the V allele of the A142V polymorphism were associated with high DBP only in male hypertensive individuals (7). Martinez Cantarin et al. (18) found a significant relationship between the A486V variant and HT in their study in African Americans. They observed that (TT) and (CT) genotypes increased the risk of HT compared to (CC) genotypes. In their study, no significant relationship was found between GRK4 R65L or A142V variants and HBP. Bengra et al. (19) also reported that the V allele of the A486V polymorphism is a risk factor for HT. Zhu et al. (20,21) found a strong interaction between age and the R65L polymorphism for SBP in their study of White and African American normotensive twins. Asbarinsyah et al. (22) determined an association between the GRK4 A486 V gene polymorphism and hypertension in the rural population of Indonesia . Our study conducted in a Turkish population indicates to a relationship between the GRK4 gene (A142V and A486V) polymorphisms and EHT. When the two polymorphisms were compared, the A142V polymorphism was found to be more significant than the A486V polymorphism in the hypertensive group. Furthermore, the A142V polymorphism was more significant in males than females. To our knowledge, our study is the first to report the frequency of GRK4 polymorphism in the Turkish population.

Conclusion

Essential hypertension is a multifactorial disorder and many genes have been implicated as potential risk factors. The association between genetic variants of the human GRK4 γ and EHT have been demonstrated by previous investigators. These studies pointed to some ethnic differences in Caucasian, American Blacks and Chinese Han populations. Our study performed in a group of Turkish subjects shows that A142V and A486V variants of the GRK4γ gene are associated with essential hypertension. The present study is limited in terms of the small sample of NT and EHT subjects. Hypertensive subjects consisted of an older group than normotensive subjects; furthermore, the number of female subjects was smaller than the males. Further studies with larger samples of EHT subjects are needed to clarify the role of A142V and A486V gene polymorphisms in EHT in the Turkish population.

Declarations

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Conflict of interest: No potential conflict of interest relevant to this article was reported. Ethics: This study was approved by Ethics Committee of Marmara University School of Medicine. (25.06.2009 and AEK: 483 number of approval.

Availability of data and material (data transparency): Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions: Sample collection from controls and patients: YD, ÖG. Experiments were performed by: HY, HC, BK, OO, CN. Results were analyzed and research was conducted by: HY, HC, BK.

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