C825T polymorphism of the G-protein β_3 subunit and its association with essential hypertension in Uzbek males

Özbek erkeklerinde G protein β_3 altbirimi C825T polimorfizmi ve esansiyel hipertansiyon ile ilişkisi

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ABSTRACT

Objectives: We investigated the association between the C825T polymorphism of the G-protein β_3 subunit (GNB_3) gene with essential hypertension (EH) and cardiovascular remodeling markers in Uzbek males.

Study design: The study included 174 Uzbek men (mean age 49±10 years) with untreated EH of stage 1-2 and 60 normotensive males. The C825T polymorphism of the GNB_3 gene in the patient and control groups was determined by polymerase chain reaction. The patients were assessed with blood pressure measurements, ambulatory blood pressure monitoring, body mass index (BMI), carotid artery intima-media thickness (IMT), flow-mediated dilation (FMD) of the brachial artery, echocardiography, and urinary albumin excretion (UAE) level.

Results: The frequencies of the CC, CT, and TT genotypes were 36.8%, 53.5%, and 9.8% in hypertensive men, and 0%, 83.3%, and 16.7% in healthy men, respectively (p=0.0001). The frequencies of the C and T alleles were 63.8% and 36.2% in the hypertensive group, and 41.7% and 58.3% in the control group, respectively (p=0.0001). The CC genotype exhibited a significantly greater risk for hypertension compared to CT and TT genotypes (OR=72.38, 95% CI 4.40-1190.34). The C825 allele showed a higher association with hypertension in comparison to the 825T allele (OR 2.41, 95% CI 1.58-3.68). Compared to patients with the CT+TT genotypes, the CC genotype carriers had significantly higher BMI (p=0.0001), systolic (p=0.0001) and diastolic (p=0.003) blood pressures (SBP/DBP), higher nighttime DBP (p=0.042), a greater nighttime variability in both SBP and DBP (p=0.002), and greater carotid artery IMT (p=0.0001) and UAE (p=0.015) values.

Conclusion: Our findings show a significant association between the GNB_3/C825T gene polymorphism and EH, with the CC genotype exhibiting higher blood pressure, BMI, and vascular remodeling markers in Uzbek hypertensive men.

ÖZET

Amaç: Çalışmamızda, Özbek erkeklerinde G protein β_3 altbirimi (GNB_3) geninde C825T polimorfizmi ile esansiyel hipertansiyon (EH) ve kardiyovasküler yeniden biçimlenme belirteçleri arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya tedavi edilmemiş derece 1-2 EH olan 174 Özbek erkek (ort. yaş 49±10) ve normotansif 60 erkek alındı. Hasta ve kontrol gruplarında GNB_3 geninde C825T polimorfizmi polimeraz zincir reaksiyonu ile belirlendi. Ayrıca, hasta grubu, kan basıncı ölçümü, ambulatuvar kan basıncı izlemi, beden kütle indeksi (BKİ), karotis arter intima-media kalınlığı (İMK), brakiyal arter akım aracılı dilatasyon (AAD), ekokardiyografi ve idrar albümin atılımı ile değerlendirildi.

Bulgular: Hipertansif erkeklerde CC, CT ve TT genotipleri sıklığı sırasıyla %36.8, %53.5 ve %9.8 bulunurken, kontrol grubunda %0, %83.3 ve %16.7 bulundu (p=0.0001). C ve T alel sıklıkları hipertansif grupta sırasıyla %63.8 ve %36.2, kontrol grubunda %41.7 ve %58.3 idi (p=0.0001). CT ve TT genotipleri ile karşılaştırıldığında, CC genotipi hipertansiyon için anlamlı derecede daha yüksek riski temsil etmekteydi (OO=72.38, %95 GA 4.40-1190.34). 825T aleli ile karşılaştırıldığında, C825 alelinin hipertansiyonla daha yakın ilişkisi vardı (OO=2.41, %95 GA 1.58-3.68). CT+TT genotip grubuna göre, CC genotipi taşıyıcılarında şu parametreler anlamlı derecede daha yüksek bulundu: BKİ (p=0.0001), sistolik (p=0.0001) ve diyastolik (p=0.003) kan basınçları, gece diyastolik kan basıncı (p=0.042), sistolik ve diyastolik kan basınçlarında gece değişkenliği (p=0.002), karotis arter İMK (p=0.0001) ve idrar albümin atılımı (p=0.015).

Sonuç: Bulgularımız, hipertansif Özbek erkeklerinde GNB_3/C825T gen polimorfizmi ile EH arasında anlamlı ilişki olduğunu ve CC genotipinde kan basıncı, BKİ ve vasküler yeniden biçimlenme belirteçlerinde artış olduğunu göstermiştir.

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Guanine nucleotide-binding proteins (G-proteins) comprise a family of ubiquitously distributed signal-transduction proteins. G-proteins are influenced by hormones and neurotransmitters and act to regulate blood pressure. Most membrane receptors rely on heterotrimeric G-proteins to activate or inhibit intracellular signaling cascades.[1] The main role of G-protein is to translate signals from the cell surface into a cellular response. The gene encoding the G-protein β_3 subunit is located on chromosome 12p13. Polymorphisms of the G-protein β_3 subunit gene have received considerable attention as a candidate gene for essential hypertension. Siffert et al.[2] detected a novel polymorphism of cytosine/thymine substitution at 825 nucleotide position (825C/T) in exon 10, of the gene encoding the β_3 subunit of the heterotrimeric G-proteins. An increased activity of the Na^+-H^+ exchanger has been noted in up to half of patients with EH. The C825T polymorphism in the G-protein β_3 subunit gene was initially discovered as a putative cause of the enhanced Na^+-H^+ exchanger activity in hypertensive patients.[3] Many studies have reported a significant association of the T allele of the GNB_3 gene with variations in blood pressure levels.[1-5] Therefore, the association of the GNB_3 polymorphism with EH may be plausible and of potential clinical and scientific relevance.

The aim of the present study was to investigate the distribution and association of the C825T polymorphism of the GNB_3 gene with EH and cardiovascular remodeling markers in Uzbek population.

PATIENTS AND METHODS

The study included 174 ethnic Uzbek men (mean age 49±10 years) with untreated EH of stage 1-2 (WHO, 2003) and age-matched 60 healthy males (mean age 41±10 years). Recruitment of patients dated back to 2004-05 as part of State Grant A-9-138. The diagnosis of EH was based on the 2003 WHO/ISH criteria on the management of hypertension.

Exclusion criteria were symptomatic hypertension, clinical evidence for cerebrovascular or coronary heart diseases, cardiac arrhythmia, heart failure, renal impairment, diabetes mellitus, metabolic and other background diseases, and alcohol intake more than 30 g pure ethanol per day. To exclude the effects of estrogenic modulations of endothelium function, women were not enrolled.

All patients gave informed consent, and the Ethics Committee of the Republican Specialized Center of Cardiology approved the study.

Seated (office) blood pressure was measured three times with a random-zero sphygmomanometer (by Korotkoff), and the last two measurements were averaged. Body mass index was calculated from height and weight measurements (kg/m^2).

Abbreviations:

ABPM Ambulatory blood pressure monitoring
BMI Body mass index
BP Blood pressure
EH Essential hypertension
FMD Flow-mediated dilation
GNB_3 G-protein β3 subunit
IMT Intima-media thickness
LVH Left ventricular hypertrophy
LVM Left ventricular mass
PCR Polymerase chain reaction
UAE Urinary albumin excretion

Gene polymorphism analysis

Blood samples were taken in the morning after an overnight fasting. A total 234 individuals were genotyped. Genomic DNA was extracted from peripheral blood using the Diatom DNA Prep 200 Kit according to the manufacturer's protocol. Polymerase chain reaction, PCR-restriction fragment length polymorphism-based techniques and visualization were performed according to previously described methodologies to determine the C825T polymorphism of the GNB_3 gene with the use of the following primers:[3] 5'-TGA CCC ACT TGC CAC CCG TGC-3' (sense); 5'-GCA GCA GCC AGG GCT GGC-3' (antisense).

The PCR product was digested with the restriction enzyme BseDI (Fermentas, Vilnius, Lithuania). The digests were then subjected to electrophoresis on a 2.5% agarose gel and visualized under ultraviolet illumination, where the undigested product (TT genotype) showed a band of 268 bp, and the completely digested PCR product (CC genotype) generated two bands of 116 bp and 152 bp, and heterozygotes (CT genotype) were displayed by the three bands mentioned above (Fig. 1).

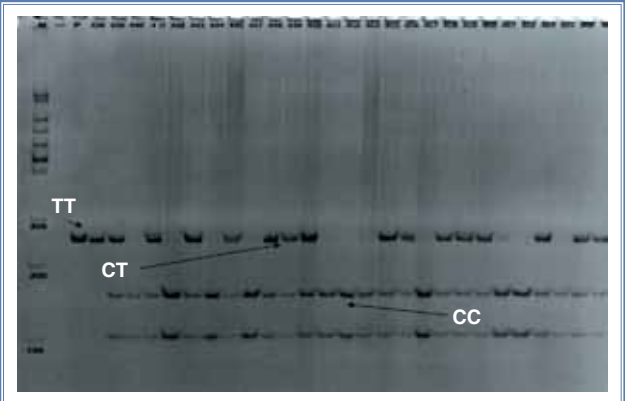

Figure 1. Visualization of the genotypes for C825T polymorphism of the GNB_3 gene under ultraviolet illumination.

Ultrasound measurements for carotid artery intima-media thickness

To measure carotid artery intima-media thickness, all ultrasound studies were done at approximately 8:00 A.M. in a temperature-controlled room (25 °C) with the fasting subject resting in the supine position using a 7.5 MHz high-resolution ultrasound (EnVisor-C, Philips, Netherlands). The measurements were obtained using longitudinal projections approximately 2 cm below the bifurcation at the starting point of the bulbus. Despite the recent guideline,[6] IMT was defined as the maximum thickness at the region of interest detected in both left and right carotid arteries including the common carotid artery.

Assessment of endothelial function

Flow-mediated dilation of the brachial artery has been widely used as a simple and noninvasive method of determining endothelial function. The diameter of the brachial artery was measured from two-dimensional ultrasound images, with a 7.5 MHz linear array transducer and a standard EnVisor-C system. In each study, scans were taken at rest and during reactive hyperemia. Reactive hyperemia was calculated as the maximum flow recorded in the first 60 sec after cuff deflation divided by the flow during the baseline scan. Flow-mediated dilation was estimated as the percent change in the diameter relative to the baseline diameter at rest and FMD of ≥10% was taken as the norm threshold as proposed by Celermajer et al.[7]

Echocardiography

Central hemodynamic parameters and left ventricular mass were estimated using M-mode echocardiography. Left ventricular mass was indexed to body surface area (g/m^2) to calculate LVM index,[8] and left ventricular hypertrophy was defined as an LVM index of ≥125 g/m^2.

Ambulatory blood pressure monitoring

Daily blood pressure profile was assessed by 24-hour ambulatory blood pressure monitoring using the TONOPORT V system (GE Medical Systems, Freiburg, Germany) in 113 patients with EH at baseline without drug therapy. Blood pressure was measured every 15 minutes in daytime and 30 minutes in nighttime.

Definition of microalbuminuria

Microalbuminuria was defined as urinary albumin excretion between 20 and 200 mg/l as determined on a Daytona autoanalyzer by the immunoturbidimetric assay.

Statistical analysis

Continuous variables were expressed as mean± standard deviation and categorical variables as percentages. Differences in continuous variables between cases and controls were examined using the unpaired Student's t-test, where the Mann-Whitney U-test was used in case of abnormal distribution. Deviations from the Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by the chi-square test with 1 degree of freedom, whereas differences in genotype distributions were assessed by the chi-square test with 2 degrees of freedom. Associations between alleles or genotypes and EH were sought using odds ratios (OR) with 95% confidence intervals. The significance level for all the analyses was set at $p<0.05$. Statistical analyses were performed using Microsoft Office Excel 2007 and Statistica v6.0 (StatSoft, USA) software.

RESULTS

Genotype and allele frequencies of the GNB_3 gene in hypertensive subjects and healthy controls are shown in Table 1. The distribution of all alleles and genotypes were within the Hardy-Weinberg equilibrium. The frequencies of the CC, CT, and TT genotypes were 36.8%, 53.5%, and 9.8% in hypertensive men, and 0.0%, 83.3%, and 16.7% in healthy men, respectively (p=0.0001). The frequencies of the C and T alleles were 63.8% and 36.2% in the hypertensive group, and 41.7% and 58.3% in the control group, respectively (p=0.0001). In the additive heritage model, the CC genotype exhibited a significantly greater risk for hypertension compared to CT and TT genotypes (OR=72.38, 95% CI 4.40-1190.34). Multiplicative mode of inheritance showed a higher association of the C825 allele with hypertension in comparison to the 825T allele (OR 2.41, 95% CI 1.58-3.68).

Partly because of the low frequency of the TT genotype, patients with the CT and TT genotypes were combined as CT+TT genotypes for further comparison with the CC genotype (Table 2). The mean age of the patients with the CC genotype tended to be higher (p=0.057). The CC homozygous group had a significantly higher BMI (p=0.0001). Systolic and diastolic blood pressures in office measurements were significantly higher in the CC genotype carriers (p=0.0001 and p=0.003, respectively). Carotid artery IMT and UAE values were also significantly greater in the CC carriers (p=0.0001 and p=0.015, respectively). Left ventricular mass index and FMD of the brachial ar-

Table 1. Genotype* and allele frequencies of the GNB_3 gene polymorphisms and associations with essential hypertension**

		Hypertensives (n=174)		Controls (n=60)					
		n	%	n	%	χ^2	*p*	OR	95% CI
Genotypes	CC	64	36.8	0	0.0	23.39	**0.0001**	72.38	4.40 - 1190.34
	CT	93	53.5	50	83.3			0.20	0.09 - 0.44
	TT	17	9.8	10	16.7			0.24	0.24 - 1.38
Alleles	C	111	63.8	25	41.7	17.12	**0.0001**	2.41	1.58 - 3.68
	T	63	36.2	35	58.3			0.41	0.27 - 0.63

*Additive heritage model (Cochran-Armitage test, x_i=[0,1,2], degree of freedom=1); **Multiplicative heritage model (chi-square test, degree of freedom=1).

tery were similar in patients with CC and CT+TT genotypes (p>0.05).

Allelic analysis showed a significant difference between C and T alleles in BMI (29.6±4.2 *vs*. 28.1±5.7 kg/m^2, p=0.006) and a tendency for higher DBP in C allele carriers (102.7±9.4 *vs*. 100.8±8.7, p=0.066).

The results of 24-hour ABPM are summarized in Table 3. Compared with the CT+TT-genotypes, patients with the CC genotype had a significantly higher nighttime DBP (p=0.042) and a greater nighttime variability in both systolic and diastolic BPs (p=0.002).

DISCUSSION

In the present study, we investigated the association between genotype variants of the C825T/GNB_3 gene and EH and cardiovascular remodeling markers in Uzbek population. We found that the C825T polymorphism of the GNB_3 gene was associated with EH and cardiovascular markers such as BMI, IMT of the common carotid artery, and the level of UAE in Uzbek hypertensive patients.

Essential hypertension induces structural and functional changes in arteries that thicken and become less compliant over time, increasing greatly the risk for atherosclerosis. It is considered to be a multifactorial disorder with many genetic, environmental, and demographic factors contributing to blood pressure variation. Genetic epidemiological studies have provided evidence that several genetic variants increase the risk for hypertension.[9]

G-proteins comprise a family of ubiquitously distributed signal-transduction proteins. Most membrane receptors rely on heterotrimeric G-proteins to activate

Table 2. Baseline characteristics of hypertensive patients with the CC and CT+TT genotypes of the GNB_3 gene polymorphisms

	CC genotype (n=65)	CT+TT genotypes (n=109)	*p*
Mean age (years)	51.1±8.9	47.9±11.5	0.057
Duration of essential hypertension (years)	6.3±3.01	6.0±4.8	NS
Smoking status (n, %)	27, 41.5%	42, 38.5%	NS
Body mass index (kg/m^2)	31.6±4.8	28.4±5.1	**0.0001**
Systolic blood pressure (mmHg)	166.9±20.0	157.3±15.0	**0.0001**
Diastolic blood pressure (mmHg)	105.5±10.6	100.8±9.1	**0.003**
Left ventricular mass index (g/m^2)	161.8±32.0	161.0±32.0	NS
Flow-mediated dilation (%)	4.6±5.7	3.4±5.7	NS
Carotid artery intima-media thickness (mm)	1.1±0.2	1.0±0.2	**0.0001**
Urinary albumin excretion (mg/l)	38.8±52.7	25.4±16.8	**0.015**

NS: Not significant.

Table 3. The results of 24-hour ambulatory blood pressure monitoring

	CC genotype (n=46)	CT+TT genotypes (n=67)	*p*
Blood pressure variability (mmHg)			
Daytime			
Systolic blood pressure	15.5±3.0	15.2±4.4	NS
Diastolic blood pressure	15.1±3.9	15.5±4.5	NS
Nighttime			
Systolic blood pressure	16.3±4.6	12.7±3.7	**0.002**
Diastolic blood pressure	14.4±3.5	11.0±3.8	**0.002**
Mean blood pressure (mmHg)			
Daytime			
Systolic blood pressure	150.3±15.3	148.0±17.8	NS
Diastolic blood pressure	104.7±13.5	101.2±14.1	NS
Nighttime			
Systolic blood pressure	142.8±23.6	140.7±20.4	NS
Diastolic blood pressure	99.6±27.3	91.0±15.8	**0.042**

or inhibit intracellular signaling cascades. G-proteins are influenced by hormones and neurotransmitters and act to regulate blood pressure. Polymorphisms of the GNB_3 gene have received considerable attention as candidate genes for EH. Many studies reported significant associations between the GNB_3 C825T polymorphism and hypertension, as well as hemodynamic phenotypes such as renal perfusion, LVH, LV diastolic filling, and coronary vasoconstriction.[2,3,10,11] Significantly higher frequencies of the 825T allele have also been reported in three independent studies in subjects with EH compared to unselected normotensive control subjects of European origin;[2,3,12] however, other studies have reported different findings.[13,14] Siffert et al.[2] demonstrated a significant association of the 825T allele with EH in a study of 426 hypertensive and 427 normotensive control subjects, the T allele frequency being higher in hypertensive (31%) than in normotensive subjects (25%). Alioğlu et al.[15] investigated 209 patients with EH and 82 subjects with normal blood pressure, Caucasians of Turkish descent. They found a significant association between the C825T gene polymorphism of the G protein and hypertension in Turkish population. The frequency of the 825T allele was 43% in normotensive and 52% in hypertensive Turkish subjects. In individuals of African descent, the 825T allele of the GNB_3 gene was reported to be a susceptibility factor for the development of hypertension.[16] Poch et al.[11] showed that the 825T allele of the GNB_3 gene was associated with increased DBP, LVM, and LVH in patients with EH. In the HARVEST Study (Hypertension and Ambulatory Recording Venetia Study), patients carrying the 825T allele had an increased risk for reaching the blood pressure end-point (need for antihypertensive therapy) during a mean follow-up of 4.7 years.[17] Investigation in an ethnic group from the United Arab Emirates demonstrated a strong association of the GNB_3 825T allele with LVH but not with EH, and high prevalences of the TT genotype (27%) and T allele (55%) in patients with EH.[18] Carriers of the 825T allele in a Southern German population had a higher BMI and percentage body fat compared with no carriers of this allele.[19] In a Japanese population, Izawa et al.[20] demonstrated an association between hypertension and the C825T polymorphism of the CNB_3 gene in male subjects. Even though allele frequencies of the 825T variant were found to be higher in Japanese (49.0% to 49.6%) compared with reported prevalences of 25% to 31% in whites, it was suggested that this particular polymorphism was uninformative in Japanese individuals.[14,21]

A separate analysis of two case-control studies from Northern Ireland and France showed no significant differences in allele and genotype frequencies between hypertensive patients and normotensive control subjects, and the C825T polymorphism was not related to age, systolic and diastolic BPs, or BMI in hypertensive subjects.[13] In another study, left ventricular dimensions, parameters of the diastolic function, and serologic markers of LVM were not associated with

the C825T variant.[22] Shlyakhto et al. [23] also found no association between LV structure or function and the GNB_3 gene variant in a St. Petersburg population. In a genetically isolate Kazakh population from northeast China, the C825T polymorphism of the GNB_3 gene did not confer a significantly increased risk for the development of EH.[24]

In the present study, we found a significant association between the C825T polymorphism of the GNB_3 gene and EH in Uzbek population. In our study, the prevalence of the 825T allele was higher in healthy subjects (58.3%) than in hypertensive patients (36.2%).

Our study has several limitations. The number of patients and controls were limited for the research and data on salt intake or salt sensitivity were lacking to explain the physiological role of the G protein polymorphism. Another limitation was that the healthy men were included as controls only for comparison of genotype and allele frequencies of the C825T polymorphism of the GNB_3 gene. Nonetheless, this is the first report examining the relationship between the C825T polymorphism of the GNB_3 gene and EH and cardiovascular remodeling markers in Uzbek population.

In conclusion, we found a significant association between the C825 allele and CC genotype of the C825T/GNB_3 gene and EH in Uzbek hypertensive patients, with significant differences in cardiovascular remodeling markers such as BMI, IMT of the common carotid artery, and UAE levels between patients with the CC genotype and CT+TT genotypes. Concerning BP, carriers of the CC genotype had significantly higher office systolic and diastolic BPs, higher nighttime diastolic BP, and a greater variability in nighttime systolic and diastolic BPs. To our opinion, our results are only preliminary and further large case-control studies in our and other Central Asia populations are needed to confirm this association. Moreover, further studies are needed to precisely define the biochemical mechanisms by which enhanced G-protein signaling may contribute to the development of hypertension.

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Key words: Blood pressure/genetics; genetic predisposition to disease; genotype; heterotrimeric GTP-binding proteins/genetics; hypertension/epidemiology/genetics; polymorphism, genetic; risk factors; Uzbekistan/epidemiology.

Anahtar sözcükler: Kan basıncı/genetik; hastalığa genetik yatkınlık; genotip; heterotrimerik GTP-bağlama proteini/genetik; hipertansiyon/epidemiyoloji/genetik; polimorfizm, genetik; risk faktörü; Özbekistan/epidemiyoloji.