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Original scientific article

GENETIC VARIANTS OF ENDOTHELIAL NITRIC OXIDE SYNTHASE (eNOS4a/b) AND SUSCEPTIBILITY TO RENAL CELL CARCINOMA IN A TURKISH POPULATION

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Nitric oxide (NO), plays a significant part in biological processes. Endothelial nitric oxide synthase (eNOS), the enzyme that catalyzes the generation of NO in endothelium, contains genetic polymorphisms that have been linked to an increased risk of developing cancer. The purpose of this investigation was to ascertain whether there is any connection between renal cell carcinom (RCC) and the *eNOS 4a/b* gene polymorphism. This study included 94 patients (mean age:54.2±10.5 years) diagnosed with histopathologically confirmed RCC and 188 healthy controls (mean age:56.7±11.1 years). *eNOS 4a/b* gene polymorphism was examined in DNA samples taken from patients and healthy controls using polymerase chain reaction (PCR) and agarose gel electrophoresis methods. The patient and control groups did not differ statistically significantly in terms of age or body mass index. The most frequent genotype of *eNOS 4a/b* gene polymorphism is bb genotype in a Turkish population. When compared to the control group, patients with RCC had significantly higher rates of the aa and ab genotypes (p= .018 and p= .000, respectively). There was no discernible difference in the *eNOS 4a/b* gene polymorphism between

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patients with high-grade and advanced-stage disease and those with low-grade and stage disease. We suggest that the *eNOS 4a/b* gene polymorphism may be effective in the onset of renal cell cancer, but it is not effective in development.

Keywords: eNOS 4a/b, nitric oxide, polymorphism, polymerase chain reaction, renal cell carcinoma

INTRODUCTION

The malignant tumor known as renal cell carcinoma (RCC) develops from the renal tubular epithelium (COURTHOD *et al*., 2015). It ranks as third after prostate and bladder cancers amongst all urogenital cancers and constitutes approximately 3% of all developing cancers (FERLAY *et al*., 2015). RCC development is caused by a number of risk factors; including smoking, obesity, hypertension, and chronic kidney disease. These risk factors are known to cause oxidative stress by raising reactive oxygen species (ROS) (GAGO-DOMINGUEZ *et al*., 2002).

Nitric oxide (NO) is a free radical synthesized by the NOS isoforms [endothelial (e), neuronal (n) and inducible (i)] during the conversion of L-arginine into L-citrulline (FORSTERMANN *et al*., 2012). Numerous physiological and physiopathological processes; such as vasodilation, immunity, neuronal signaling, smooth muscle relaxation and carcinogenesis, are influenced by nitric oxide (VAHORA *et al*., 2016; EHRENFELD *et al*., 2019). However, the available data about the tumor predisposing and suppressing role of NO is inconsistent. Certain studies showed that NO- produced in high amounts forms peroxynitrite ($ONOO^-$), interacting with superoxide. This formed peroxynitrite can cause DNA mutations by interacting with DNA directly or inhibiting DNA repair enzyme activities (CHIEN *et al*., 2004). There are some studies suggesting that NO supports tumor angiogenesis and metastasis (MARROGI *et al*., 2000; JADESKI *et al*., 2003; DUDA *et al*., 2004). Contrary to this, some studies showed that the endothelial production of NO affects tumor pathogenesis positively, regulates blood stream and angiogenesis and prevents tumor cells to adhere to the endothelium (XU *et al*., 2002; DHAR *et al*., 2003; FABBRI *et al.*, 2005).

The eNOS gene, which has 26 exons and 25 introns, is found on the 7q35-36 chromosome (ALDERTON *et al*., 2001). In the Single Nucleotide Polymorphism DataBase, the eNOS gene has been found to have more than 168 polymorphisms (dbSNP). Many studies have been conducted on the relationship between the *eNOS gene's intron 4a/b* polymorphism and several cancer types, including colorectal, bladder, and prostate cancers (YEH *et al*., 2009; AMASYALI *et al*., 2012; MEDEIROS *et al*., 2002; SANLI *et al*., 2011). As far as we know, there is no research studying the connection between *eNOS intron 4a/b* polymorphism and RCC.

In view of these facts, the goal of this study was to examine the impact of the *eNOS intron 4a/b* gene polymorphism on the risk factors and clinicopathological traits of RCC in the Turkish population.

MATERIALS AND METHODS

Study subjects

94 patients (mean age 54.2±10.5 years) who applied to Urology policlinic of Istanbul Faculty of Medicine and diagnosed with RCC clinically and histopathologically were included in study group. 188 healthy individuals (mean age 56.7±11.1 years) applied to the same department

for various urological symptoms enrolled as control group. All participants were informed through written informed consent forms and necessary permission was obtained from Ethics Committee of Istanbul Faculty of Medicine.

Prior to study inclusion, all subjects underwent thorough medical evaluations and physical examinations. There was no history or indication of a second malignancy in the patients. None of the patients had carcinogen and heavy metal exposure past. The patients did not use any antoxidant or vitamin-mineral supplements including selenium during the study. The selected people' ages, sexes, BMIs, and smoking habits were noted. Smokers were defined as those who currently smoked or had quit smoking within the past year, while non-smokers were those who had never smoked or had quit within the past year. By dividing the weight (kg) by the square of the height (m^2), the body mass index (BMI) was determined.

According to the WHO/ISUP grade classification system and the 2017 TNM staging system, the patients' grades and clinical T stages were determined. Grades 1-2 were accepted as low and Grade 3-4 as high grade tumor. T1-T2 stages were regarded as low stage and T3-T4 as high stage tumor in a similar way. Histopathological cancer types of all patients were clear cell cancer.

Genotyping

Venous blood samples belonging to the patients and healthy group were taken into blood tubes containing EDTA. Using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany), total genomic DNA isolation was carried out on the samples. Prior to usage, obtained DNA samples were kept at a temperature of –20 °C. To find the *eNOS intron 4a/b* gene polymorphism, we applied the PCR method described by WANG et al. (1996). DNA samples multiplied by using spesific primer sequences for intron 4 domain. Primers were 5'- AGG CCC TAT GGT AGT GCC TTT -3' (forward) and 5'- TCT CTT AGT GTG GTC AC -3' (reverse). 100 ng DNA, 10 x PCR tampons (pH: 8.75), 2.5 mM MgCl2, 0.25 mM for each dNTP, 25 pmol for each primer, and 1.5 U Taq Polymerase were included in the reaction mix. PCR conditions were arranged as 60 sec denaturation at 94 °C, 60 sec binding at 56 °C and 2 minutes elongation at 72°C for 35 cycles. PCR products were separated at ethidium bromide stained 2 percent agarose gel by electrophoresis.

Statistics

Software called SPSS 21 was used to conduct statistical analyses. Data on clinical variables were presented as mean±SD. Clinical parameters analyzed by using Mann-Whitney U test for unequal variances and Student t-test for equal variances.

Chi-square test was used to evaluate the distribution of eNOS gene mutations and allele frequencies between RCC patients and the control group. The presence of an independent connection between RCC and genetic variation was investigated using multiple logistic regression analysis after correcting for factors such as age, gender, body mass index (BMI), and smoking history. Calculated as a measure of the link between eNOS genotypes and RCC, adjusted odds ratio (aOR) [95 percent confidence interval (CI)]. Results with p values less than .05 ($p < .05$) were considered significant. The Hardy-Weinberg equilibrium (HWE) was

supported by the genotypes of *eNOS 4a/b* in both the study and control groups (p= .08 and p= .33, respectively).

RESULTS

Age, sex, BMI, or smoking status did not differ between RCC patients and controls in a statistically meaningful way (Table 1).

Table 1. Clinical traits of RCC patients and those in the control group

Parameters	Controls (n=188)	Patients (n=94)	p value*
Age (years)	56.7±11.1	54.2±10.5	.076
BMI (kg/m²)	27.3±2.8	28.3±4.9	.052
Sex (%) (female/male)	25.5/74.5	31.9/68.1	.259
Smoking status (%) (current/never)	61.7/38.3	53.2/46.8	.171

* From the Mann-Whitney U test or Student's t test for continuous variables and the chi-square test for categorical variables.

The genotype distribution of the *eNOS 4a/b* gene polymorphism differed significantly between control group and the RCC patients. In comparison to participants with the bb genotype, those with the ab and aa genotypes had an approximately 2.09-fold (aOR 2.09, 95 percent CI 1.13 - 3.85, p= .018) and 4.52-fold (aOR 4.52, 95 percent CI 2.01 - 10.17, p= .000) greater risk for RCC. Additionally, those who had at least one mutant an allele (aa or ab) had a 2.73-fold higher risk of developing RCC than those who had homozygotes for bb (aOR 2.73, 95 percent CI 1.53 - 4.87, p= .001). The frequency of the a-allele was also shown to be significantly higher than the b-allele in the RCC group in comparison to the control group (aOR 2.78, 95 percent CI 1.85 - 4.18, p= .000) (Table 2).

Table 2. Genotype distributions and eNOS 4a/b polymorphism allele frequencies in controls and RCC patients

	Controls n (%)	Patientsn (%)	p value*	aOR (95% CI) †
Genotypes				
bb	131 (69.7)	44 (46.8)		Reference
ab	54 (28.7)	35 (37.2)	.018	2.09 (1.13-3.85)
aa	3 (1.6)	15 (16)	.000	4.52 (2.01-10.17)
ab + aa	57 (30.3)	50 (53.2)	.001	2.73 (1.53-4.87)
Allele				
b	316 (84)	123 (65.4)		Reference
a	60 (16)	65 (34.6)	.000	2.78 (1.85-4.18)

* The chi-square test was used to compare the genotype distributions and allele frequencies and to determine the p value.

† [a]OR and 95% CI adjusted for sex, age, smoking status, and BMI.

Our findings showed that in patients with RCC, the *eNOS4a/b* gene polymorphism was not related to grade or stage (Table 3).

Table 3. According to the tumor grade and T stage, the eNOS 4a/b gene polymorphism's genotype distribution and allelic frequency

	Low grade[a] n (%)	High grade[b] n (%)	p value	[a]OR (95% CI) †
Genotypes				
bb	29 (48.3)	15 (44.1)		Reference
ab	24 (40)	11 (32.4)	.393	.59 (.18-1.94)
aa	7 (11.7)	8 (23.5)	.520	1.26 (.61-2.59)
ab + aa	31 (51.7)	19 (55.9)	.720	.83 (.30-2.28)
Allele				
b	82 (68.3)	41 (60.3)		Reference
a	38 (31.7)	27 (39.7)	.265	1.42 (.76-2.64)
	Low T stage[c] n (%)	High T stage[d] n (%)	p value	[a]OR (95% CI) †
Genotypes				
bb	29 (48.3)	15 (44.1)		Reference
ab	23 (38.3)	12 (35.3)	.952	1.03 (.33-3.18)
aa	8 (13.4)	7 (20.6)	.175	1,64 (.80-3.37)
ab + aa	31 (51.7)	19 (55.9)	.546	1.35 (.50-3.61)
Allele				
b	81 (67.5)	42 (61.8)		Reference
a	39 (32.5)	26 (38.2)	.426	1.28 (.69-2.39)

[a] Low grade (G_1+G_2); [b] High grade (G_3+G_4); [c] Low stage (T_1+T_2); [d] High stage (T_3+T_4)

† [a]OR and 95% CI adjusted for sex, age, smoking status, and BMI.

DISCUSSION

Genetic and environmental variables have been linked to the development of renal cell carcinoma (LINDBLAD, 2004; CAPITANIO *et al*., 2019).There are studies showing that single nucleotide polymorphisms (SNPs), among the genetic influences, may be associated with susceptibility to urogenital carcinomas (SUN *et al*., 2008; STADLER *et al*., 2010).

After the discovery of NO in 1987, many studies have been conducted on the relationship between NO and cancer and it has been determined that NO may be effective both in the formation and in the progression of the cancer that has already formed. It has been suggested that NO causes this by increasing DNA damage and inhibiting DNA repair enzymes (CHIEN *et al*., 2004). Researches have revealed that increased amounts of NO lead to the production of RNOS such as superoxide, peroxinitrite and cause DNA damage through these reactive substances (BLAISE *et al*., 2005; BURLAKA *et al*., 2015; WANG *et al*., 2017). In addition, it has been shown

that NO inhibits the activities of many DNA repair enzymes by deamination of the DNA bases encoding them (BLAISE *et al*., 2005; MUZALOV *et al*., 2015). However, in another study; it has been demonstrated that NO protects the cell from DNA damage, as well as has an anti-tumor effect by reducing the adhesion of tumor cells to the endothelium by upregulation of poly (ADP ribose) polymerase (PARP) and DNA-dependent protein kinase (DNA-PK) (XU *et al*., 2002). The disparate sensitivity of tumor cells to NO-mediated cytostasis or apoptosis can be used to explain these inconsistent findings reported in the literature (JADESKI *et al*., 2002).

The eNOS gene's intron, exon, and promoter regions have all been found to contain different polymorphisms. A functional polymorphism with 4 consecutive 27 base pair repetitions in the a allele and 5 in the b allele is present in the *intron 4a/b* gene. The relationship of *eNOS intron 4a/b* polymorphism with various cancer types has been

investigated in many studies, but conflicting results were obtained.

YEH *et al*. (2009) found that patients under 60 years old were particularly at risk for developing colorectal cancer with early start when they had the intron 4a mutant genotype. The aa genotype is substantially more common in people with superficial bladder cancer, according to a different study by AMASYALI *et al*. (2012), who also observed that those with the ab+aa genotype were more likely to experience tumor development and recurrence.

In their study, MEDEIROS *et al*. (2002) found that having the a-allele increases the probability of prostate cancer development, high-grade tumors, and progression. SANLI *et al*. (2011) found that patients carrying a-allele had a higher risk of tumor progression and metastasis although they did not find a relationship between prostate cancer risk and *eNOS intron 4a/b* gene polymorphism.

HEFLER *et al*. (2002) found that at least one mutant allele of intron 4 is related to an advanced tumor stage in patients with ovarian cancer, while RIENER *et al.* (2004) found that the allelic variation in intron 4 affects disease-free survival in patients with vulvar cancer.

Contrary to these studies, in a recent study, KOCER *et al.* (2020) found that patients with epidermoid lung carcinoma had a significantly higher b allele frequency (p= .036) and bb genotype (p= .021) distribution compared to the control group. Similarly, in a study conducted in patients with breast cancer suggested that mutant a-allele and homozygous mutant aa genotype reduced breast cancer risk .878 and .194 times, respectively (TAHMASEBI, 2020). As far as we know, there is no study examining *eNOS intron 4a/b* polymorphism in patients with RCC.

In this study, we found that in the patient group with RCC, those who carried at least one a allele had a 2.73 times higher risk than those with the bb genotype, and this risk was found significant (p= .001). According to certain research, the eNOS gene locus may have a role in variations in the genetic regulation of plasma NO synthesis. The a-allele is linked to lower NO levels than the b-allele (TSUKADA *et al*., 1998; SONG *et al*., 2003). Accordingly, we suggest that aa genotype of *eNOS 4a/b* gene polymorphism related to lower NO production may play a stronger role in tumor growth and therefore be effective in the formation of renal cell carcinoma.

To further understand the connection between eNOS gene polymorphisms and RCC formation and progression, large-scale patient investigations are required.

CONCLUSION

In conclusion, we discovered that the Turkish population had a higher prevalence of the bb genotype of *eNOS intron 4a/b* gene polymophism. Additionally, the RCC patient group had considerably higher levels of the genotypes ab and aa as well as the a-allele than the control group did. Our findings indicate that the *eNOS intron 4a/b* gene polymorphism may be a risk factor for the initiation of RCC, but not for its development.

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GENETIČKE VARIJANTE ENDOTELIJALNE SINTAZE AZOTOKSIDA (eNOS4a/b) I OSETLJIVOST NA KARCINOM BUBREŽNIH ĆELIJA U TURSKOJ POPULACIJI

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Izvod

Azot oksid (NO) igra značajnu ulogu u biološkim procesima. Endotelna sintaza azot oksida (eNOS), enzim koji katalizuje stvaranje NO u endotelu, sadrži genetske polimorfizme koji su povezani sa povećanim rizikom od razvoja raka. Svrha ovog istraživanja bila je da se utvrdi da li postoji bilo kakva veza između karcinoma bubrežnih ćelija (RCC) i polimorfizma gena eNOS 4a/b. Ova studija je obuhvatila 94 pacijenta (srednja starost: 54,2±10,5 godina) sa dijagnozom histopatološki potvrđenog RCC i 188 zdravih kontrola (srednja starost:56,7±11,1 godina). Polimorfizam gena eNOS 4a/b je ispitivan u uzorcima DNK uzetim od pacijenata i zdravih kontrola primenom metoda PCR i elektroforeze u agaroznom gelu. Grupa pacijenata i kontrolna grupa nisu se statistički značajno razlikovale u pogledu starosti ili indeksa telesne mase. Najčešći genotip polimorfizma gena eNOS 4a/b je bb genotip u turskoj populaciji. U poređenju sa kontrolnom grupom, pacijenti sa RCC su imali značajno veće stope genotipova aa i ab (p= .018 i p= .000, respektivno). Nije bilo vidljive razlike u polimorfizmu gena eNOS 4a/b između pacijenata sa visokom i uznapredovalom stadijumom bolesti i onih sa bolešću niskog stepena i stadijuma. Može se zaključiti da polimorfizam gena eNOS 4a/b može biti efikasan u nastanku raka bubrežnih ćelija, ali nije efikasan u razvoju.

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