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Original Article

The MNS16A VNTR polymorphism of the TERT gene in bladder cancer

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ABSTRACT

Objective: Bladder cancer (BC) is a complex disease that has a high morbidity rate. The MNS16A polymorphism in the TERT gene has been indicated to play a role in the presence of various cancer types and multiple tumor populations. In the present study, our goal was to investigate whether the MNS16A (VNTRs) in the TERT gene was associated with bladder cancer.

Material and methods: A total of 70 patients with BC and 120 normal controls were included in the study. The MNS16A (VNTRs) in the TERT gene was amplified using polymerase chain reaction (PCR). The PCR products were visualized on 3% high resolution agarose gel and under a UV light.

Results: The MNS16A VNTR-302 allele was found to be the most common allele in both, the patient group (64%) and the control group (62%). The second most common allele was the VNTR-243 allele that occurred at a frequency of around 34% in BC patients and 33% in the controls. VNTR-333 (patient group, 1%; control group, 3%) and VNTR-274 (patient group, 2%; control group, 1%) alleles were reported as the least common alleles in this study.

Conclusion: When comparing the frequencies of genetic variants between cases and controls, we observed that our findings did not support the hypothesis that the MNS16A VNTR polymorphism of the TERT gene might regulate cancer susceptibility.

Keywords: Bladder cancer; MNS16A (VNTR) polymorphism; TERT gene.

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Introduction

Bladder cancer (BC) is a commonly seen urologic cancer that has a serious morbidity and mortality rate and a high cost of treatment. Environmental exposures to carcinogens (e.g., tobacco) are the important factors that increase an individual's risk of developing BC. Bladder cancer is the 9th most common malignant disease in the world and the 13th leading cause of cancer-related deaths worldwide. A total of 429,793 BC cases were diagnosed in 2012, and about 165,000 of these were recorded as deaths globally. The disease is more likely to affect men than women, and its incidence increases with aging. Bladder cancer usually originates from the urothelium, i.e., the inner surface epithelium of the bladder. The most common type of bladder cancer is urothelial carcinoma. According to the genome-wide copy number analysis, in up to 20% of the cases, deletions on regions 10q, 11p, 11q, 17p, 18q, 19p, and again in 19q have been reported, however, high-level DNA amplification has been indicated as a rare event in this tumor group.[1]

Telomeres are present at the ends of chromosomes and help to maintain the integrity of the genomic structure.[2] They consist of a single-stranded extension and protein complex with tandem nucleotide repeats of the hexamer (TTAGGG)n.[3,4] Telomeres are functional units that prevent chromosome degradation and stop fusions and rearrangements in eukaryotic chromosomes.[5-7] Human telomerase reverse transcriptase gene (hTERT) is present in region 5p15.33 and encodes a ribonucleoprotein enzyme that extends chromosome ends that get shortened at each cell division.[6]

Control of telomerase action and telomere length have been reported to be closely related to tumor formation in humans. Recent evidence suggests that genetic variation for the 5p15.33 region of the TERT gene might play a role in regulating the risk of cancer development.[8-10] Mutations in coding regions of the TERT gene have important effects on telomerase activity and telomere length.[8,11] Moreover, these mutations might also cause serious clinical phenotypes in syndromes with bone marrow failure and increase cancer frequency.[8,12] Studies have reported the effects of TERT gene variants as increased risk of hematological malignancies, such as cancer of the blood or lymphoid tissues.[8] Other evidence from GWAS studies has also shown that there is a strong association between the locus at 5p15.33 and some cancers, such as adenocarcinoma[13], basal cell carcinoma, pancreatic cancer[14], and lung cancer.[15-17] In addition, "risky" alleles in this region have been reported to be significant for the occurrence of glioma[18,19], bladder cancer[20,21], and prostate cancer.[22] Activating mutations in the core promoter of the TERT gene are the most common mutations to have ever been identified for bladder cancer, and show a ratio of 55.6-82.8%. Furthermore, these mutations have been found to be independent of the stage and grade of the disease.[21]

For the time in the literature, polymorphic tandem repeat minisatellites of TERT, called MNS16A, were reported in a study with lung cancer.[23] MNS16A was indicated as an antisense copy of the TERT gene located in its promoter region.[24] The MNS16A variable number tandem repeat (VNTR) functional polymorphism has been investigated in many studies such as nasopharyngeal carcinoma[5], colorectal cancer[6,24], lung cancer[23-25], prostate cancer[24,26], and in the normal human life span.[7,27] In this study, we aimed to determine the effect of MNS16A VNTR polymorphism of the TERT gene in the risk of bladder cancer in a Turkish population.

Material and methods

Study population

The population for the present study included 70 patients with BC (65 males and 5 females, mean patient age=62.34±9.52 years) and 120 unrelated healthy volunteers (97 males and 23 females, mean age=61.08±11.59 years) as controls (Table 1). BC patients (37 smokers, 33 non-smokers) were in an age range of 36-81 years and the control group subjects (34 smokers, 86 non-smokers) were in an age range of 37-94 years (Table 1). These subjects (case-control) were studied retrospectively and were randomly recruited from the Urology clinic of Nigde and Luleburgaz State Hospital, Turkey. The type of BC in all patients had been diagnosed as transitional cell carcinoma and confirmed by histopathological examination. The study was approved by the Local Ethics Committee of Kocaeli University (KU GOKAYEK 2016/93), and all retrieval of patients' approvals were obtained from patients who participated in this study.

Genotyping and allele confirmation

Genomic DNA was purified from peripheral venous blood leucocytes using the QIAamp DNA Blood Mini Kit (Maryland, USA). A polymerase chain reaction (PCR) was used to amplify the genomic variants for MNS16A VNTR polymorphism by using appropriate primers. The forward primer sequence was 5'-AGGATTCTGATCTCTGAAGGGTG-3' (sense) and the reverse primer sequence was 5'-TCTGCCTGAGGAAGGACGTATG-3' (antisense).[28] The PCR protocol was as follows; an initial denaturation at 95°C for 5 minutes, followed by denaturation for 35 cycles at 95°C for 30 seconds, and annealing at 60°C for 30 seconds, at 72°C for 1 minute, and at 72°C for 10 minutes. The PCR products were visualized on 3% high resolution agarose gel (100 V for 75 V) under a UV transilluminator using Safe-T staining (ethidium bromide alternative).[17] In this study, we observed four different-sized alleles including VNTR-302, VNTR-243, VNTR-274, and VNTR-333, of which VNTR-302 was a wild-type allele.

Table 1. Demographic characteristics of bladder cancer (BC) patients and controls

Parameters	Patients n=70	Controls n=120	p	OR (95% CI)
Age (years±SD)	62.34±9.52	61.08±11.59		
Age range	(36-81)	(37-94)	0.20	
Sex (%)				
Male	65 (92.6)	97 (80.8)	0.03*	3.08 (1.11-8.52)
Female	5 (7.4)	23 (19.2)		
Smoking status (%)				
Smoker	37 (52.9)	34 (28.3)	0.001*	0,.338 (0.181-0.630)
Non-smoker	33 (47.1)	86 (71.7)		

p<0.05: significantly different from control group; SD: standard deviation; OR: odds ratio; CI (95%): confidence interval

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Statistical analysis

Genotype distributions of MNS16A VNTR polymorphisms for the study samples were tested for the Hardy-Weinberg equilibrium (HWE) using the Chi-square (χ^2) test. Differences in the distribution of demographic characteristics and the alleles and genotypes of the MNS16A VNTR polymorphism between BC patients and controls were compared by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis. The relationship between the MNS16A VNTR genotypes and the risk of BC was assessed by calculating odds ratios (OR) and the 95% confidence intervals (CI) from logistic regression analysis with and without possible confounding factors (gender as a nominal variable and age and smoking as continuous variables). For the reference category, the most common genotype of the MNS16A VNTR polymorphism was used. Single alleles, genotypes, and the SL (S, short; L, long variant alleles) classification system were used for calculations. S was used for VNTR-243 and VNTR-274, while L was used for VNTR-302 and VNTR-333. P<0.05 was considered statistically significant. The analyses were performed using Statistical Package for the Social Sciences software version 17.0 (IBM SPSS Corp.; Armonk, NY, USA).

Results

In the present study, a total of 190 subjects (70 BC patients and 120 controls) were studied. Selected demographic characteristics of the patient and control groups are demonstrated in Table 1. There was no significant difference in the mean age between BC patients and control groups. However, there were statistically significant differences between the two groups with respect to gender (p=0.03; OR=3.08; 95% CI=1.11-8.52) and smoking status (p=0.001; OR=0.333; 95% CI=0.181-0.630) (p<0.05). These differences were then controlled by multivariate analysis. In the study, the BC group consisted of 65 men and 5 women, while the control group had 97 men and 23 women. Genotype frequencies observed for MNS16A (VNTR) polymorphism were in accordance with Hardy-Weinberg's equilibrium (HWE) in BC patients (p=0.76; χ2=0.091), but deviated from HWE in the controls (p=0.04; χ2=4.131).

The results of genotyping are shown in Table 2, and four different sizes of MNS16A (VNTR) alleles (302, 243, 274 and 333) were analyzed. Of these alleles, the VNTR-302 allele was found to be the most common allele in both, the patient

Table 2. The genotype and allele frequencies of MNS16A VNTR polymorphism in bladder cancer patients and controls

			Crude values		Adjusted values (smoking and age)	
TERT MNS16A	**Cases n=70**	**Controls n=120**	**p**	**OR CI (95%)**	**p**	**OR CI (95%)**
Allele (%)						
302 alleles	89 (64)	148 (62)		1.00		
243 alleles	46 (33)	81 (34)	0.821	1.059 (0.677-1.656)		
274 alleles	3 (2)	2 (1)	0.371	0.401 (0.066-2.446)		
333 alleles	2 (1)	9 (3)	0.223	2.706 (0.572-12.808)		
Genotype (%)						
302/302	28 (40)	42 (35)		1		1
302/243	30 (43)	59 (49)	0.414	0.763 (0.398-1.460)	0.511	0.797 (0.406-1.566)
243/243	7 (10)	8 (7)	0.635	1.312 (0.428-4.028)	0.589	1.368 (0.439-4.261)
333/243	1 (1.4)	4 (3)	0.391	0.375 (0.040-3.533)	0.341	0.335 (0.035-3.174)
333/302	1 (1.4)	5 (4)	0.283	0.300 (0.033-2.707)	0.301	0.311 (0.034-2.847)
243/274	1 (1.4)	2 (2)	0.818	0.750 (0.065-8.671)	0.650	0.557 (0.045-6.974)
302/274	2 (2.8)	0 (0)	-	-	-	-
Group of genotype (%)						
LL	29 (41)	47 (39)		1		1
SL	34 (49)	65 (54)	0.573	0.836 (0.447-1.561)	0.635	0.854 (0.445-1.639)
SS	7 (10)	8 (7)	0.499	1.441 (0.500-4.153)	0.343	1.700 (0.568-5.085)

p<0.05: Significantly different from control group; OR: odds ratio; CI (95%): confidence interval; L: long; S: small

group (64%) and the control group (62%). The second most common allele was the VNTR-243 allele that occurred at a frequency of around 33% in BC patients and 34% in the controls. On the other hand, VNTR-333 (patient group, 1%; control group, 3%) and VNTR-274 (patient group, 2%; control group, 1%) alleles were reported to be the least common alleles in this study (Table 2). In the study, the genotype frequency for 302/302 was 40% in BC patients and 35% in controls, whereas for 302/243 it was 43% in BC and 49% in controls, with the 302/302 genotype being used as the reference group. Additionally, 333/243, 333/302, 243/274, and 302/274 genotypes were very rare genotypes, and each one was found only once or twice. In this study, no significant difference was found on comparing the frequencies of genotypes between patients and controls (Table 2). Even when these genotypes were grouped as LL, SL, and SS, there were no significant differences between them.

Discussion

At present, high telomerase activity is perceived as one of the distinctive characteristics for human cancers.[20] In a study, telomerase was reported to play an important role in the development and progression of lung cancer.[17] In other studies, functional polymorphisms affecting expression or activity of this gene were shown to increase the susceptibility pf the patient for bladder cancer.[20,21] In the present case-control study, we investigated the association between the MNS16A VNTR polymorphism and BC patients in a Turkish population. We observed four types of alleles, i.e., VNTR-302, VNTR-243, VNTR-274, and VNTR-333. A study on colorectal cancer also reported the presence of four VNTR MNS16As of TERT in an Austrian society, of which VNTR-302 had the highest frequency.[6] In our results, we found that none of the alleles were important for the studied population.

The relationships between the MNS16A VNTR polymorphism and human cancers have been investigated in various studies. In one study, it was reported that the VNTR-243, VNTR-272, and VNTR-302 alleles were associated with increased breast cancer risk in a Chinese population, as were the genotypes of 302/271, 302/243, and 243/243 (OR=1.50, 95% CI=1.15–1.96), as compared to the wild-type 302/302 genotype.[28] In another study, it was found that white Spanish patients with glioblastoma multiforme exhibited a worse survival rate in comparison to genotypes having at least one VNTR-302 or VNTR-333 allele against homozygous genotypes of the VNTR-243 or VNTR-272 alleles.[29] In another study, it was detected that TERT variants were not associated with overall survival, however, it was reported that patients with S alleles had a shorter survival rate than patients with non-small cell lung cancer (NSCLC).[25]

In China, researchers of another study compared the allelic and genotypic frequencies of MNS16A polymorphism in 446 cases (90 years and older) with those in 332 controls (22-53 years) and did not find any significant differences between the groups.[7] In another Danish study with the same gene variants, the relationship of TERC and four TERT SNPs with leukocyte telomere length (n=864) and longevity (n=1069) with the ages of 58 years and 100 years was investigated and no association was found.[30] In contrast, the TERT MNS16A L/L genotype was reported to be related to increased longevity in an Italian population.[27]

For the first time, VNTRs for MNS16A were investigated in colorectal, lung, and prostate cancer cell lines using the luciferase reporter assay, and VNTRs were found to exhibit higher promoter activity in all the cell lines examined.[24] MNS16A VNTRs were also examined in colorectal cancer patients, and it was found that the frequency of the VNTR-274 allele was increased 2.7-fold as compared to the wild types seen on the VNTR-302 allele.[6] In another study on MNS16A polymorphism, no significant difference between prostate cancer patients and controls with benign prostatic hyperplasia was identified. However, by using stratified analysis, it was found that the MNS16A VNTR-274 allele and the 274/302 genotype were associated with a reduced risk in prostate cancer patients who were aged 70 years and older.[26] In the present study, the distributions of MNS16A VNTR alleles and genotypes between patients and controls were not different.

Genetic polymorphisms often show ethnic differences. In our study, the frequencies of the VNTR-302, -243, and -274 alleles in healthy controls were 0.620, 0.340, and 0.010, respectively. These values for healthy Austrians were 0.652, 0.316, and 0.016, respectively. The frequencies of VNTR-302, -272, and -243 alleles in Koreans were 0.944, 0.030, and 0.025, respectively[17], while those in a Chinese population were 0.947, 0.012, and 0.041, respectively.[28] The frequencies of alleles that we found for our population were observed to be closer to those in the Austrian population, but quite different from the Korean and Chinese populations.

Our results reveal that there is no relationship between the TERT gene MNS16A VNTR polymorphism and the susceptibility to bladder cancer. On the other hand, this study is limited due to its small sample size and it might not be sufficient to clarify the relationship between this polymorphism and BC. However, this research is important in terms of being the first study to investigate these gene variants in a bladder cancer patient group. Similar studies conducted in larger and more diverse ethnic populations will contribute to verifying the results of this study. As a conclusion, further studies are needed to explain the relationship between MNS16A VNTR polymorphism and bladder cancer.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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