The Association of *MYNN* and *TERC* Gene Polymorphisms and Bladder Cancer in a Turkish Population

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Purpose: Researchers reported that, *MYNN* rs10936599 polymorphism is in strong or moderate linkage disequilibrium with SNPs within the 3q26.2 chromosomal regions that also include the *TERC* gene. In addition, it has been reported that *MYNN* rs10936599 had a strong cumulative association with bladder cancer risk, and *TERC* gene suppresses cell growth in bladder cancer cell lines. Therefore, we aimed to determine whether polymorphisms of *MYNN* rs10936599 and *TERC* rs2293607 play any roles for bladder cancer in the Turkish population in this study.

Materials and Methods: In this case-control study, 70 patients and 150 controls were investigated. Genotyping analysis was performed by polymerase chain reaction, restriction fragment length polymorphism and DNA sequencing techniques.

Results: Genotype distribution between study groups for MYNN rs10936599 SNP was significantly different (P = .001); although there was no difference in genotype distribution for *TERC* rs2293607 SNP. In addition, patients with CT genotype and CT+TT genotype combination of *MYNN* SNP have a decreased risk for bladder cancer. Two times increased risk ratio on development of bladder cancer was obtained for CC genotype of the SNP (P = .001). Besides, it was found that genotype combination of GG+AG/CC versus AA/CC genotypes (*TERC/MYNN*) showed stronger correlation. We observed that statistically significant relationship between the C-G haplotypes of two polymorphisms and bladder cancer risk (P = .0001).

Conclusion: At the end of the study, we suggested that there may exist an association between a combination of MYNN rs10936599 and *TERC* rs2293607 polymorphisms and development of bladder cancer in Turkish population.

Keywords: Bladder cancer; *MYNN* gene; polymorphism; *TERC* gen

INTRODUCTION

Bladder cancer (BC) is a major problem and, 11th most common cancer in the world[(1)]. BC is higher in men than women, and its incidence increases with age for both gender, peaking at the seventh decade[(2)]. Genetic and potential environmental factors play role in the etiology of the disease and, familial cancer history increasing risk of BC. In addition, there is important heterogeneity in terms of its clinical and genetic backgrounds of urothelial carcinomas and, the heterogeneity partly originates from different changes in different genes that affect various mechanisms associated with cell proliferation and cancer[(3, 4)]. A genome-wide association studies (GWAS) have informed that new locus on chromosome (chr) 3q may be correlated with BC risk. In addition, it has been reported that the locus on chromosome 3q is included in MYNN gene and TERC gene and, these genes are strong candidates for the association with bladder cancer[(4)].

Myoneurin (MYNN) gene locates on 3q26.2 and encodes a member of the BTB/POZ and zinc finger (ZF) domain-containing protein family that is involved in the control of gene expression[(5)]. Certain polymorphic regions were discovered on the MYNN gene. The rs10936599 polymorphism is one of these regions. The function of rs10936599 polymorphism on the MYNN gene is not known. Some research concludes that this synonymous variation is associated with both longer telomeres and the colorectal cancer or patients with adenomas[(6-8)]. Additionally, it has been suggested that the MYNN polymorphism may be associated with ovary and bladder cancers[(5,9)]. Furthermore, the variation which is close to Telomerase RNA component (TERC) gene participates at least partly in tumorigenesis at early stages[(7,10)].

Telomerase is a specialized ribonucleoprotein polymerase that adds TTAGGG repeats to telomere ends in soma human cells, including stem cells. The holoenzyme consists of a protein component with reverse transcriptase (TERT) activity, and a RNA component (TERC). The TERT utilizes the TERC as a template to add repeats to the existing telomeres [(7, 11)]. The TERC is a 451 base pairs (bp) long gene, located on chromosome 3q26.2. TERC is a template for telomeric DNA

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Table 1. Demographic characteristics of bladder cancer patients and controls

Parameters	Patients n = 70 (%)	Controls n = 150 (%)	*p* value	OR (95% CI)
[a]Age year ± SD (age range)	61.95 ± 10.63 (25-81)	59.41 ± 12.92 (22-94)	.15	
[b]Sex			.09	
Male	61 (87.1)	118 (78.7)		
Female	9 (12.9)	32 (21.3)		
[b]Smoking status			.002*	2.55 (1.42-4.58)
Smoker	36 (51.4)	44 (29.3)		
Non-smoker	34 (48.6)	106 (70.7)		

Abbreviation: ±SD, Standard derivation;
*$p < .05$; significantly different from control group;
[a]Continuous variables were compared by independent samples t-test;
[b]Categorical variables including sex and smoking status were compared by chi square test.

synthesis. Besides, it has the same important roles including catalysis, accumulation, localization and holoenzyme assembly [12]. Telomerase is up-regulated in the majority of human cancers. The increased telomerase activity is thought to be required to allow tumor cells to divide after genetic rearrangements enabled by telomere dysfunction[13]. Consistent the data, Soder et al. (1997) reported that the level of TERC expression increases with tumor progression. It has been known that gene polymorphisms may cause significant changes in enzyme activity[14]. According to remarkable data in the study of Figueroa and co-workers (2014), it has been reported that the rs10936599 SNP is in complete Linkage Disequilibrium with SNP rs2293607. *TERC* has been appeared to affect telomere length and mRNA folding in several functional studies. Based on the literature, no study has investigated the association of *TERC* rs2293607 polymorphism and BC risk. Until now, there has been no study investigating the effects of *MYNN* rs10936599 and *TERC* rs2293607 polymorphisms on BC risk. Therefore, we aimed to determine whether *MYNN* gene rs10936599 and *TERC* rs2293607 polymorphisms that were closely located on 3q26.2 play any roles in the bladder cancer in a Turkish population.

MATERIALS AND METHODS

Study Population: The patients and controls were selected among the ones from urology clinic of Luleburgaz and Niğde State Hospital, Turkey. We investigated the *MYNN* rs10936599 and *TERC* rs2293607 SNPs (Single Nucleotide Polymorphisms) in 70 bladder cancer patients and 150 healthy controls. Protocol of the present study was reviewed and approved by the institutional review board of the Local Human Ethics Committee (Decision number: KAEK 2014/144). Informed consent was submitted by all subjects when they were enrolled.

Inclusion and exclusion criteria: Patient group was generated with individuals who have been diagnosed bladder cancer by histopathological examination. Bladder cancer type of all patients is transitional cell carcinoma. Patients, who have received any chemotherapy or radiotherapy, were not accepted in the study. The control group matched with age and gender distributions of patients was selected from healthy volunteers without bladder cancer history.

DNA Isolation and Genotyping: Genomic DNA was extracted from the whole blood treated with EDTA using the QIAamp DNA Blood Mini Kit (Maryland, USA), according to the manufacturer's guidelines. PCR amplifications of both the polymorphic regions in *MYNN* and TERC genes were using specific primer sets (for MYNN rs10936599 polymorphism F:5'- TCAAGGGTAAAATTCCATTCTG-3' and R:5'- TCACAGAGAAAACCTGCTTCC-3'; for TERC rs2293607 polymorphism F:5'-AGTTCGCTTTCCTGTTGG-3' and R:5'- ATTCATTTTGGCCGACTT-3').

The PCR was performed in a final reaction volume of 20 µl containing 10 ng of genomic DNA, 10 pmol of each primer, 5x FIREPol Master Mix (Solis BioDyne). PCR reaction was made on these conditions: after initial denaturation at 95°C for 5 minutes, then followed by 38 cycles including of denaturation at 95°C for 40 seconds for denaturation, 58°C in the rs10936599 polymorphism, 59°C in the rs2293607 polymorphism for 30 seconds for annealing, and 72°C for 30 seconds for extension. The reaction was completed by a final extension of 5 min at 72°C.

Evaluations: SNP rs10936599 is a point mutation occurring with C → T substitution at nucleotide 18 in *MYNN* gene and, this mutation causes coding of a synonymous variant (His6His). SNP rs2293607 is a point mutation occurring with A → G substitution at nucleotide 514 in TERC gene (15). PCR products of *MYNN* and *TERC* polymorphic regions were digested with HpyCH4III at 37°C for over-night and BsrDI at 65°C for 30 min, respectively. PCR products were separated by electrophoresis on 2% agarose gels, and visualized under ultraviolet (UV) illumination after nucleic acid staining solution (ECO Safe). The PCR product size for *MYNN* rs10936599 SNP was 104 base pair (bp) and the wild-type allele (C) contains two fragments of 58 and 46 bp. The polymorphic variant (T) was seen a fragment of 104 bp. PCR product size for TERC rs2293607 SNP, was 159 bp. After enzymatic digestion of these products, the fragment sizes were 94 bp and 65 bp for the wild type (A). A fragment of 159 bp was seen for the variant allele (G).

Statistical analysis: The genotype and allele frequencies of two SNPs were tested for Hardy-Weinberg Equilibrium using a chi-square ($\chi 2$) test. Deviations from Hardy-Weinberg equilibrium (HWE) were analyzed by using Michael H. Court's (2005-2008) online calculator. On the result of power analysis which was performed for detecting an association between BC and the studied polymorphisms, sample sizes were found to

Table 2. The Genotypes and allele frequencies of MYNN (rs10936599) C/T and TERC (rs2293607) A/G genes SNPs in bladder cancer patients and control Individuals in Turkish population

Gene cGenotypes	Patients n = 70 (%)	Controls n = 150(%)	[d]Crude values *P* value	OR CI (95%)	[e]Adjusted values *P* value	OR CI (95%)
***MYNN* (rs10936599)**						
CC	46 (66)	63 (42)		1		
CT	19 (27)	78 (52)	.001*	0.33 (0.17-0.62)	.15	2.45 (0.71-8.41)
TT	5 (7)	9 (6)	.77	0.76 (0.23-2.42)	.78	0.84 (0.25-2.77)
CT+TT	24 (34)	87 (58)	.001*	0.37 (0.20-0.68)	.003*	2.53 (1.38-4.63)
Alleles						
C	111 (79)	204 (68)		1		
T	29 (21)	96 (32)	.01*	0.55 (0.34-0.89)		
TERC (rs2293607)						
AA	27 (39)	68 (45)		1		
AG	39 (55)	77 (51)	.45	1.27 (0.70-2.29)		
GG	4 (6)	5 (4)	.44	2.01 (0.50-8.07)	.27	0.71 (0.38-1.30)
AG+GG	43 (60)	82 (55)	.38	1.32 (0.74-2.35)	.35	0.50 (0.12-2.11)
Alleles						
A	93 (66)	213 (71)		1		
G	47 (34)	87 (29)	.37	1.23 (0.80-1.90)		

[c]Distributions of genotypes in groups were compared by chi square test; dCrude values of odds ratios were calculated by Fisher exact test; eIndependent variables were compared by logistic regression. Adjusted with smoking habit and gender Adjusted values of odds ratios were calculated by using the statistic method. *$P < .05$ indicates statistically significant.

be sufficient for case and control groups consisting of 70 and 150 individuals (α: 0.05, β: 0.20 and test power; 0.80). Statistically analysis of demographic feature was performed via student's t-test and chi-square tests by using SPSS version 18. The frequencies of genotype and allele for these two SNPs in patients and controls were compared using Cochrans's and Mantel-Haenszel statistics test. For each polymorphism, unconditional logistic regression was used to calculate adjusted (with smoking habit and gender) odds ratios (OR) in 95% confidence intervals (95% CI) for BC. $P < .05$ value was considered as statistically significant. EH program was used for analysis of haplotype frequencies.

RESULTS

The demographic characteristics of patients and controls were demonstrated on **Table 1**. When frequencies of mean age and gender were compared in both groups, the control group was found to be compatible with patients (for mean age $P = .051$, for gender $P = .09$). Smoker count in patient group (51.4%) compared with those in controls was found significantly higher ($P = .002$).

Frequencies of genotype and allele for two polymorphisms in patient and control groups were shown in **Table 2**. Genotype distribution of *MYNN* rs10936599 SNP among both groups was different and, the value was statistically significant ($P = .001$). In addition, patients with CT genotype and CT+TT genotype combination versus CC genotype and T allele versus C allele of the *MYNN* polymorphism compared those with controls have a decreased odds ratio for BC. Similar odds ratio was also obtained when the heterozygous genotype together with other risk factors such as gender and smoking habit were evaluated. All these data are illustrated in **Table 2**. Interestingly, the frequency of CC genotype (wild type for rs10936599) in patients was higher than one in controls. When CC genotype was compared to other genotypes of the MYNN polymorphism among case-control groups, approximately 2 times increased odds ratio between BC development and this genotype was found [$P = .001$, OR = 2.64 (1.46-4.77)].

Frequencies of genotypes (AA, AG, GG) and alleles (A and G) for TERC rs2293607 polymorphism were observed as 38.6, 55.7, 5.7% and 66.4, 33.6% in patients, respectively and 45.3, 51.3, 3.3% and 71, 29% in controls, respectively. For the TERC SNP, we detected that GG genotype versus AA genotype resulted in odds ratio of two fold, but the ratio was not statistically significant ($P = .44$).

In addition, gene-gene interaction and haplotype analysis among cases and controls were made in the study. It was observed in gene-gene interaction analysis that genotype combination of GG+AG/CC (TERC gene/MYNN gene) versus wild type genotypes of two polymorphisms (AA/CC) revealed stronger correlation (Table 3). Besides, four possible haplotypes of MYNN (rs10936599) and TERC (rs2293607) SNPs were identified in our study. C-A haplotype was accepted as a reference haplotype because it was more common in two groups. For the two variants, a linkage was found in both patients and controls ($\chi 2 = 24.09$, $P = .0001$ for patients; $\chi 2 = 178.77$, $P = .0001$ for controls). We obtained statistically significant relationship between patients and controls for the C-G haplotypes ($P = .0001$) (**Table 3**).

There is no data about histological types and stage of patients with bladder cancer, so these parameters were not evaluated in the study.

DISCUSSION

MYNN rs10936599 and *TERC* rs2293607 SNPs in 70 bladder cancer patients and 150 healthy controls were analyzed in this current study. In our study, genotype distributions in controls for two polymorphisms were not compatible with the principle of HWE. The cause of the drift from HWE is selection from hospital-based individuals of control group in this study. In addition, we evaluated as reference allele, so C allele for the MYNN gene polymorphism is wild type in the current study.

Table 3. Analysis of gene- gene interaction and haplotype for MYNN (rs10936599) and TERC(rs2293607) polymorphisms

Gene Genotypes	Patients n (%)	Controls n (%)	*P* value	OR CI (95%)
MYNN gene (rs10936599)/TERC gene (rs2293607)				
CC-AA	24 (52.2)	62 (98,4)		1
CT/AA	3 (15.8)	6 (7.7)	.71	1.29 (0.29-5.58)
CT/AG	16 (84.2)	72 (92.3)	.15	0.57 (0.28-1.17)
TT/AG	1 (20)	4 (44.4)	1	0.64 (0.06-6.07)
TT/GG	4 (80)	5 (55.6)	.44	2.06 (0.51-8.35)
CT+TT/AA	3 (11.1)	6 (8.8)	.71	1.29 (0.29-5.58)
GG+AG/CC	22 (47.8)	1 (1.6)	.0001*	56.8 (7.25-445.3)
CT+TT/GG+AG	21 (46.7)	81 (56.6)	.30	0.67 (0.34-1.31)
MYNN gene (C/T)/TERC gene (A/G) Haplotypes				
C A	45	100		1
C G	11	20	.0001*	12.22 (2.60-57.42)
T A	2	6	1	0.74 (0.14-3.81)
T G	12	42	.29	0.63 (0.30-1.32)

*$P < .05$ indicates statistically significant.

However, for rs10936599 SNP, more of the individuals with C allele were obtained in patients compared to controls in our study. Therefore, all genotypes without pointing out a reference allele were analyzed again. We obtained significant odds ratio for CC genotype for bladder cancer among patients (these data were not shown on table). We suggest that T allele may have a protective effect in spite of C allele for bladder cancer. As consisted with our data, in a genome wide association studies (GWAS), Wang et al., (2014) reported that C allele of MYNN rs10936599 polymorphism may entail a risk for bladder cancer and the SNP together with other polymorphic side may be used, collectively, to effectively measure inherited risk for bladder cancer (16). Besides, it has been reported that T allele for rs10936599 polymorphism at 3q26.2 shows a protective effect on bladder cancer in another GWAS by Figueroa et al., (2013) (ORadj per T allele = 0.85, 95% CI 0.81-0.90 and $p = 4.53x10-9$)[4].

When the effect of the polymorphism in other cancer species has been investigated, similar results were detected. Carvajal-Carmona et al. (2013) examined some SNPs in colorectal cancers. They found that rs10936599 SNP of the MYNN gene was associated with adenoma risk[8]. At the same time, in a GWAS studies conducted by Huolston et al., (2010), Lubbe et al., (2012), and Real et al., (2014), rs10936599 polymorphism was found risky in colorectal cancers[9,17,18]. Furthermore, Speedy et al., (2014) identified new susceptibility loci mapping to 3q26.2 (rs10936599) for chronic lymphocytic leukemia (CLL) in a genome-wide association study[19]. It has been reported in some studies by Houlston et al., (2010), Lubbe et al., (2012), and Kantor et al., (2014) that, C allele for rs10936599 SNP was major and risk allele in colorectal cancer[9,17, 20].

Furthermore, as similar to our finding, T allele was shown as effective allele when the association of rs10936599 SNP and telomere length for coronary heart disease (CHD) was investigated in Han Chinese population[21]. In addition, it has been found that the T allele may have a protective effect in the study OR = .907 (0.825–0.995). Telomere length was not analyzed in current study but we thought that bladder cancer risk of the polymorphism may be affected by alteration of telomere length. However, Broberg et al., (2005) reported that telomere length was significantly shorter in buccal cells from patients with bladder cancer than in control subjects. Telomere shortening increases the cancer risk rather than preventing it. It has been identified as the reason of the discrepancy in the study that short telomeres may increase the risk of developing cancer, particularly epithelial cancers via non-reciprocal translocations[22]. The reason of this discrepancy may be the effects of other genes and risk factors. Wang et al., 2014 found that seven significant variants including *MYNN* rs10936599 had a strong cumulative association with bladder cancer risk. These loci showed the potential to predict the risk of bladder cancer in combination with the smoking risk factor in the Chinese population[16]. In another study, it has been reported that this susceptibility locus rs10936599 at 3q26.2 is in linkage disequilibrium with SNPs in *TERC*. In addition, it has been suggested that *TERC* gene suppresses cell growth in bladder cancer cell lines[23]. On the other hand, it has been indicated that rs10936599 could change the regulatory elements of *MYNN* or nearby genes to discuss the bladder cancer risk[16].

Moreover, with regard to the results from a study by Jones et al. on *MYNN* and *TERC*, rs10936599 alleles were associated with both longer telomeres and colorectal cancer risk. They reported that this variation close to *TERC* probably acts at an early stage in tumorigenesis. *TERC* rs2293607 is estimated by RNA fold to change the transcript's secondary mRNA structure. Furthermore, Jones et al. stated that data from the ENCODE Project had indicated H3K4Me1 and H3K4Me3 histones in the immediate vicinity of rs2293607. Additionally, the same region is considerably sensitive to DNaseI and estimated binding site of multiple transcription factors as like NFKB, PU.1, POU3F2 and MYC[7]. Figueroa et al. (2014) found significantly higher *TERC* mRNA expression in muscle-invasive bladder tumors than adjacent normal bladder tissues[4]. According to their report, *TERC* gene may have functional relevance for predisposition to bladder cancer but the possible functional effect of the *MYNN* gene in the associated LD block cannot be excluded as a molecular cause of this association. From some GWAS studies, some researchers found that rs10936599 SNP is in strong or moderate LD with SNP within the region 3q26.2 that includes the *TERC* gene[10]. In our study, we also investigated whether there is an association between *TERC* rs2293607 (A/G) polymorphism and bladder cancer risk. No significant association was found for the poly-

morphism. We did not find any data related to the *TERC* polymorphisms and bladder cancer risk in literature. So, our findings associated with *TERC* (rs2293607) SNP were not compared. When the data related to localization of MYNN rs10936599 which is close to *TERC* genes[7] was considered, together with these *MYNN* and TERC SNPs were analyzed for bladder cancer risk in the present study. After gene-gene interaction analysis, a stronger correlation was obtained between GG+AG genotype combination for *TERC* (rs2293607) and CC genotype for *MYNN* (rs10936599) polymorphisms. It has been predicted that GG+AG combination of the TERC gene may cause telomere shortening. The remarkable finding was found consistent with those from Broberg et al. (2005)[22]. In addition, it has been shown in our study that C and G haplotypes (for *MYNN* and TERC SNPs, respectively) had odds ratio value of approximately 12 fold in development of bladder cancer.

CONCLUSIONS

We think that MYNN and TERC genes together may be associated with development of bladder cancer in the current study. In addition, establishing larger numbers of study groups, increasing the number of SNPs in the studied genes, and measuring the telomere lengths and evaluating them together will conclude more effective results.

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CONFLICT OF INTEREST STATEMENT

All authors have no potential conflicts of interest to disclose.

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