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Roles of p53 Codon 72 and miR-502-binding Site in the 3'-UTR of SET8 SNPs in Urinary Bladder Cancer Predisposition in Turkish Population

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ABSTRACT A case-control study was conducted to elucidate the possible roles of two SNPs (TP53 codon 72 and SET8 miR-502) that may affect each other in the same signaling pathway in bladder cancer susceptibility. Genotype distributions of 180 bladder cancer patients in comparison with 203 cancer-free controls were tested using PCR-RFLP method. For TP53, the researchers observed some protective effect of CC (Pro/Pro) genotype when compared with the heterozygous form (CG). For SET8 miR502, the researchers found no significant association in terms of variant alleles. These data suggest the association of TP53 codon 72 SNP, but not SET8 miR-502 with bladder cancer susceptibility in Turkish population. Further studies with larger sample sizes and different ethnicities are desirable to validate the researchers' findings.

INTRODUCTION

Extensive survey of literature revealed no study information of TP53 codon 72 (rs1042522) and SET8 miR-502 (rs16917496) SNPs together in bladder cancer up to now. In the present study, the researchers aimed to investigate the effects of both SNPs in terms of bladder cancer susceptibility and possible association with the clinicopathological data.

Urinary bladder cancer ranks ninth in worldwide cancer incidence and is the seventh most common malignancy in men and seventeenth in women (Pandith et al. 2010). Moreover, transitional cell carcinoma (TCC) of bladder is the second most common malignancy of the genitourinary tract after prostate cancer (Lin et al. 2005).

The p53 tumor suppressor gene is responsible for the maintenance of genomic stability by controlling cell cycle and facilitating DNA repair in response to DNA damage. Thus, it is known as 'the guardian of the genome' or 'the policeman of the oncogenes' with an analogous title (Levine 1997; Efeyan and Serrano 2007). Tumor suppressor TP53, located on chromosome 17p13, is one of the most commonly mutated genes in all types of human cancers including bladder cancer. Unlike other tumor suppressors that commonly undergo nonsense or frameshift mutations, SNPs are the most common genetic variants in TP53. Though certain genitourinary cancers (testis cancer, pheochromocytoma, and Wilms tumors) do not commonly manifest p53 mutations, some others (bladder and prostate cancers) are frequently associated with the alterations in p53 (Lin et al. 2005; Pandith et al. 2010; Hosen et al. 2015). TP53 somatic mutations contribute to approximately 35-72 percent of muscle-invasive bladder tumors (Pandith et al. 2010). TP53 codon 72 functional SNP in exon 4 (the substitution of G to C) results with an arginine-proline amino acid change and thus gives rise to three genotypes. The p53Arg and p53Pro proteins are reported to be biochemical-

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ly different from each other (Kietthubthew et al. 2003; Pandith et al. 2010)

MicroRNAs (miRNAs) are a class of small (~20-22 nt) noncoding RNA molecules that regulate gene expression as binding to the 3'-untranslated region (3'UTR) of targeted mRNA and play role in crucial processes such as differentiation, proliferation and apoptosis as well as the initiation, progression and metastasis of human cancers since they also function as tumor suppressors and oncogenes (Xu et al. 2013; Narouie et al. 2017). Approximately 30 percent of human genes are transcriptionally or post-transcriptionally regulated by miRNAs and SNPs in pre-miRNA or mature miRNA sequences and miRNA-binding sites may cause changes in cancer/chemotherapy susceptibility and prognosis since they result in the deregulation of target gene expression. MiR-502 binding site SNP in the 3'UTR of the histone methyltransferase SET8 gene which was taken into consideration in this study is one of these miRNA molecules. SET8 gene located on chromosome 12q24.31 has also a clearly defined function in the TP53 pathway since it monomethylates p53 at lysine 382 and suppresses the p53-mediated transcription activation of target genes (Xu et al. 2013; Hashemi et al. 2014). SET8 can also promote epithelial-mesenchymal transition (EMT) and enhance the invasive capacity of breast cancer cells via functional interdependence with transcription factor TWIST (Yang et al. 2012).

Thus, the researchers aimed to investigate the possible effects of TP53 codon 72 (rs1042522) and SET8 miR-502 (rs16917496) SNPs in terms of bladder cancer susceptibility in Turkish population.

MATERIAL AND METHODS

Recruitment of Study Participants

The study subjects included 180 cases and 203 controls. Briefly, patients with transitional cell carcinoma of the bladder were sequentially recruited from 2017 to 2019 from the Departments of Urology, before they had chemo- and/or radio-therapy. Random healthy volunteers without any history of cancer were recruited as controls. The study was approved by the Institutional Ethical Committee of Istanbul Medeniyet University (Approval number: 2017/0178).

Blood Collection and DNA Extraction

Peripheral blood samples from the participants were collected and whole blood DNA extraction was performed with Magnesia® 16 Nucleic Acid Extraction Instrument with the compatible kit to the instrument using 400 µl peripheral blood.

Genotype Analysis of the p53 Codon 72 SNP

Analysis of the p53 codon 72 SNP was carried out with PCR-RFLP method. The exon 4 of the p53 gene was first amplified by PCR with the primers previously described (Kietthubthew et al. 2003). Each PCR was done in a 25 µl reaction mixture containing ~100 ng genomic DNA, 1 µM of each primer, 0.2 mM of each dNTP, 1x PCR buffer, 2 mM $MgCl_2$, and 1.5 U of Taq polymerase (Thermo Fisher Scientific, USA). The reaction conditions were as follows: Pre-denaturation at 94°C for 9 min, then followed by 40 cycles of 94°C for 1 min; 61°C for 1 min; 72°C for 1 min and a final extension step at 72°C for 10 min completed the reaction giving rise to a 203 bp amplicon. The amplicons were then digested for 2.5 hours by the restriction enzyme *BstUI* at 37°C. The genotypes were determined by electrophoresis on 3 percent agarose gel stained with ethidium bromide under UV light. The enzyme cut the PCR product of the Arg allele into two fragments, 125 bp and 78 bp, while the PCR product of the Pro allele remained uncut. Thus, the heterozygous form has three bands at 203, 125 and 78 bp. To control whether repeat analysis is successful or not, 20 percent of randomly selected samples were genotyped again and yielded 100 percent concordance.

Genotype Analysis of the SET8 miR-502 Binding Site SNP

PCR-RFLP method was used to identify the genotype of the selected SET8 (rs16917496 C/T) SNP within the 3'-UTR. SET8 gene was first amplified by PCR protocol with the primers previously described (Song et al. 2009). PCR reaction mixture was the same as p53 amplification except for the primers. PCR profile consisted of an initial melting step of 95°C for 5 min, 35 cycles

of 95°C for 45 sec, 63°C for 40 sec, 72°C for 30 sec, and a final extension step of 72°C for 10 min. This process yielded a 308 bp amplicon, which was then digested with *SwaI* restriction enzyme at 30°C for 2.5 hours and the digested fragments were separated and analyzed on 3 percent agarose gel stained with ethidium bromide under UV light. Allele C lacks the SwaI restriction site and thus remains uncut with a single 308 bp band, while allele T produces two bands (159 bp and 149 bp). Therefore, CT heterozygote produces three bands of 308 bp, 159 bp, and 149 bp. As in the case of the p53 codon 72 SNP, we genotyped random samples (20% of the total) and found no genotyping mistake (100% match).

Statistical Analysis

Statistical analysis was done using statistical package SPSS 22 software. Data were analyzed by χ^2 test. Association between SNPs and bladder cancer was calculated by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analyses. Possible associations of SNPs with demographical and clinicopathologic characteristics in bladder cancer patients were analyzed by χ^2 -test. The statistical level of significance was defined as $p<0.05$.

RESULTS

Characteristics of Study Subjects

A total of 180 patients with transitional cell carcinoma of bladder were enrolled in this study (Table 1). Of 180 cases, 77.2 percent was >60 years and 82.8 percent was male individuals. Cigarette smoking was reported by 80.6 percent of the patients. Grade 1 carcinoma was the most abundant situation with 65 percent and the grade 2 followed this with 31.1 percent. The control group consisted of 203 healthy individuals without any history of malignant disease.

The Association between SET8 and p53 SNPs and Bladder Cancer Risk

The genotypes and allele frequencies of SET8 and p53 SNPs are shown in Table 2. The observed genotype frequencies of SET8 and p53 SNPs did not deviate from the Hardy-Weinberg equilibrium ($P<0.05$). The distribution frequencies of the rs16917496 (SET8 miR-502 binding site SNP) in bladder cancer patients and controls were compared using the χ^2- test. Compared with CC genotype, CT, TT and CT+TT genotypes did not show any association in terms of the risk analysis for bladder carcinogenesis. However, the findings for p53 codon 72 SNP revealed that CG genotype increased the risk of bladder carcinoma compared to CC genotype (OR=1.890, 95% CI=1.005-3.553, $p<0.05$).

In regard to clinicopathological characteristics and SET8 miR-502 binding site SNP, no association was found (Table 3). For p53 codon 72 SNP, there was an association in terms of grade (Table 4).

Table 1: Demographic characteristic of bladder carcinoma cases

Characteristics		*Cases (%)*
Total	180	
Age		
>60	139	(77.2)
<60	41	(22.8)
Sex		
Male	149	(82.8)
Female	31	(17.2)
Cigarette Smoking		
Ever	145	(80.6)
Never	35	(19.4)
pT		
pT1	101	(56.1)
pT2	5	(2.8)
pTa	67	(37.2)
LMPUN	7	(3.9)
Grade		
0	7	(3.9)
1	117	(65)
2	56	(31.1)
CIS		
0	169	(93.9)
1	11	(6.1)

DISCUSSION

Several studies investigating the association of p53 codon 72 SNP on cancer susceptibility were reported though the results were not consistent. The controversies may stem from the ethnic composition of the studied populations and different risk habits in various regions. Till now, there is no study in Turkish population

Table 2: Association between SET8 and p53 SNPs and bladder cancer risk

Genotype	*Cases, n (%)*	*Controls*	χ^2	*P-value*	*OR (95%CI)*
SET8					
CC	26 (14.4)	28 (13.8)			
CT	82 (45.6)	93 (45.8)	0.028	0.868	1.053(0.572-1.940)
TT	2 (40)	82 (40.4)	0.031	0.860	1.058(0.569-1.967)
CT-TT	154 60	175 (59.6)	0.033	0.855	
C allele frequency	134 0.372	149 0.367			
T allele frequency	226 0.628	257 0.633	0.022	0.881	1.023(0.762-1.372)
P53					
CC	28 15.6	23 11.3			
CG	67 37.2	104 51.2	3.966	0.046*	1.890(1.005-3.553)
GG	85 47.2	76 37.4	0.069	0.793	1.088(0.578-2.049)
CG-GG	152 (84.4)	180 (88.7)	1.476	0.224	1.442(0.797-2.607)
C allele frequency	123 0.342	150 0.369			
G allele frequency	237 0.658	256 0.631	0.642	0.423	0.886(0.658-1.192)

Table 3: Association between SET8 rs16917496 SNP and clinicopathologic characteristics

	Cases					
Variables	*n*	*CC*	*TT*	*CT*	χ^2	*P*
Age						
<60	41 (22.78%)	5	17	19	0.222	0.895
>60	139 (77.23%)	21	55	63		
Gender						
Female	31 (17.23%)	2	16	13	3.027	0.22
Male	149 (82.78%)	24	56	69		
Smoking Status						
Ever	145 (80.56%)	22	55	68	1.366	0.505
Never	35 (19.45%)	4	17	14		
Tumor Type						
pTa/LMPUN	74 (41.12%)	7	29	38	3.109	0.211
pT1/pT2	106 (58.89%)	19	43	44		
Grade						
High	56 (31.12%)	6	23	27	0.933	0.627
Low	124 (68.89%)	20	49	55		
Associated CIS						
No	169 (93.89%)	25	67	77	0.32	0.852
Yes	11 (6.12%)	1	5	5		
Tumor Size						
<3	119 (66.12%)	17	48	54	0.018	0.991
>3	61 (33.89%)	9	24	28		
Tumor Number						
Single	151 (83.89%)	22	62	67	0.562	0.755
Multiple	29 (16.12%)	4	10	15		
Recurrence						
No	117 (65%)	17	46	54	0.067	0.967
Yes	63 (35%)	9	26	28		
Progression						
No	157 (82.78%)	22	63	72	0.188	0.91
Yes	23 (12.78%)	4	9	10		
Radical Cystectomy						
No	158 (87.78%)	22	61	75	1.907	0.385
Yes	22 (12.23%)	4	11	7		
Patient Survival						
Alive	156 (86.67%)	20	63	73	2.574	0.276
Exitus	24 (13.34%)	6	9	9		

Table 4: Association between p53 rs1042522 SNP and clinicopathologic characteristics

	Cases					
Variables	*n*	*CC*	*TT*	*CT*	χ^2	*P*
Age						
<60	41 (22.78%)	3	22	16	2.82	0.243
>60	139 (77.23%)	25	63	51		
Gender						
Female	31 (17.23%)	4	15	12	0.202	0.904
Male	149 (82.78%)					
Smoking Status						
Ever	145 (80.56%)	22	68	55	0.188	0.910
Never	35 (19.45%)	6	17	12		
Tumor Type						
pTa/LMPUN	74 (41.12%)	11	37	26	0.391	0.822
pT1/pT2	106 (58.89%)	17	48	41		
Grade						
High	56 (31.12%)	16	22	18	10.501	**0.005**
Low	124 (68.89%)	12	63	49		
Associated CIS						
No	169 (93.89%)	25	81	63	1.329	0.515
Yes	11 (6.12%)	3	4	4		
Tumor Size						
<3	119 (66.12%)	14	57	48	4.193	0.123
>3	61 (33.89%)	14	28	19		
Tumor Number						
Single	151 (83.89%)	24	71	56	0.082	0.96
Multiple	29 (16.12%)	4	14	11		
Recurrence						
No	117 (65%)	21	52	44	1.79	0.49
Yes	63 (35%)	7	33	23		
Progression						
No	157 (82.78%)	25	72	60	0.916	0.632
Yes	23 (12.78%)	3	13	7		
Radical Cystectomy						
No	158 (87.78%)	23	74	61	1.536	0.464
Yes	22 (12.23%)	5	11	6		
Patient Survival						
Alive	156 (86.67%)	26	70	60	2.78	0.249
Exitus	24 (13.34%)	2	15	7		

evaluating the effects of p53 codon 72 and SET8 miR-502 SNPs together in bladder cancer.

It is now a widely accepted fact that frequencies of p53 codon 72 polymorphism may vary by ethnicity. The decreased frequency of the *Pro* allele with increased latitude, ranging from 63 percent in Africans to 50 percent in African-Americans, 29 percent in Caucasians, and 17 percent in Swedes has been reported while the frequency ranged from 35 to 40 percent in Japanese studies (Kuroda et al. 2003). This study showed that the frequency of the *Pro* allele was 11.3 percent in controls and 15.6 percent in cases, partially similar to Swedes. The reports investigating the relationship between p53 codon 72 SNP and bladder cancer offer some controversial results. Chen et al. (2000) showed the association with proline form homozygotes with invasive bladder cancer. The Pro forms of codon 72 in TP53 (Pro homozygotes or heterozygotes) were found to be related with the higher susceptibility to bladder cancer development in the Kashmiri population (Pandith et al. 2010). Lin et al. (2012) proposed Pro/Pro genotype as a progression index in bladder cancer since the genotype Pro/Pro had a 3.36-fold increased risk to develop muscle-invasive bladder cancer compared to the non-carriers. Zhang et al. (2011) reported that the p53 codon 72 Arg/Arg genotype and Arg allele were associated with lower

risk of bladder cancer in Chinese population. Kuroda et al. (2003) implied that the Pro/Pro genotype of the p53 codon 72 SNP increased the risk of urothelial cancer in smokers. The patients with Pro/Pro genotypes at position 72 were found at high risk in terms of developing bladder cancer in Bangladeshi population (Hosen et al. 2015). Contrary to these reports, individuals harboring the Arg/Arg genotype was found to have an increased risk of developing bladder cancer in Greece population. The authors also implied that the presence of the p53Arg itself in a heterozygous status was not sufficient to develop the tumor phenotype (Soulitzis et al. 2002). This study's results reflect the opposite since Pro/Arg genotype was found to be associated with increased risk for bladder cancer when compared with CC genotype (P=0.046; OR=1.890; 95%CI=1.005-3.553). Meta-analysis of association studies of p53 codon72 SNP with bladder cancer reflected a difference according to the ethnicity; while Pro/Pro genotype seemed to increase the susceptibility to bladder cancer in Asians, a significantly higher frequency of Arg/Arg genotype was found among Caucasian patients with bladder cancer compared to controls (Li et al. 2010; Xu et al. 2012). Though Arg/Arg genotype was also seen with higher frequency in cases in our study, that was not valid for the controls in whom Pro/Arg genotype was present in higher frequency. This study reflected some protective effect of Pro/Pro genotype when compared with Pro/Arg genotype. The comparison between Pro/Pro and Arg/Arg genotypes did not reflect a statistically significant association (Table 2). There were a few reports that did not reflect the association with TP53 codon 72 SNP and bladder cancer. Mabrouk et al. (2003) did not find any association between TP53 codon 72 SNP and bladder cancer in Tunisian patients. Törüner et al. (2001) previously analyzed p53 codon 72 SNP on bladder cancer susceptibility in a case control study of 121 bladder cancer patients and 114 controls in Turkish population and found no association. On the other hand, though we did not conduct an extensive analysis of literature in terms of other cancer types apart from bladder cancer for p53 codon 72 SNP, the protective effects of Pro/Pro may be possible in other cancer models and this issue needs to be clarified in depth. For instance, the pro/pro genotype has been offered to have some protective effect on oral cancer (Kietthubthew et al. 2003) in accordance with this study.

Differently from extensive studies at p53 codon 72 SNP, miRNA-502 binding site SNP in SET8 gene is a less studied gene in cancers and since the researchers' have not found such data related with bladder cancer in literature, they tried to conduct a comprehensive analysis of the effect of SET8 miR-502 binding site SNP in other cancer types. Wang et al. (2012) reported that SET8 CC genotype was associated with a decreased risk of epithelial ovarian cancer in Chinese population. In Chinese patients with hepatocellular carcinoma, SET8 CC genotype resulted in reduced SET8 protein levels was independently associated with longer postoperative survival (Guo et al. 2012). SET8 CC+CT genotype was found to be independently associated with longer survival in small-cell lung cancer patients in China (Ding et al. 2012). Xu et al. (2013) reported that CC genotype which was also found to be linked with reduced SET8 protein expression was associated with longer survival and reduced risk of death for non-small cell lung cancer in Chinese population (Xu et al. 2013). In esophageal squamous cell carcinoma patients in China, SET8 CC genotype was associated with longer post-operative survival (Wang et al. 2016). SET8 CC genotype was found to be associated with a decreased clear cell renal cell carcinoma risk compared with the CT and CT+TT genotypes in Chinese population and reduced SET8 expression based on immunostaining associated with CC genotype was also emphasized (Zhang et al. 2017). C allele was found to be associated with decreased risk of breast cancer in an Iranian population (Barjui et al. 2017). Some contradictory results exist for this SNP too as in the case of p53 codon 72 SNP. Hashemi et al. (2014) showed that CT as well as CT+TT decreased the risk of childhood acute lymphoblastic leukemia compared with CC genotype in southeast Iranian population. In a prostate cancer study again conducted in Iranian population, C allele significantly increased the risk of prostate cancer compared to T allele (Narouie et al. 2017).

To the best of the researchers' knowledge, there are only two studies in literature evaluating the combined effects of miR-502 binding site

SNP and p53 codon 72 SNP. A possible gene-gene interaction was proposed in Chinese population for non-small cell lung cancer (SET8 TT and p53 GG genotypes increased the risk in a multiply manner (OR: 3.032; 95%CI=1.580-5.816) and for cervical cancer (the combination of SET8 CC and p53 GG genotypes increased the risk in a synergistic manner (OR: 9.913; 95%CI=2.028-48.459) (Yang et al. 2014a; Yang et al. 2014b). However, the researchers' results did not reflect such a gene-gene interaction tendency in bladder cancer.

CONCLUSION

As 'the guardian of the genome', p53 gene plays a very important role in cancer studies and one of the mostly studied SNPs in this gene is p53 codon 72. SET8 gene has a defined function in the TP53 pathway and miR-502 binding site SNP in the 3'UTR of the histone methyltransferase SET8 gene has also gained importance in cancer studies. Thus, the possible effects of these SNPs in bladder cancer predisposition in different populations may be of capital importance. This study does not reflect the possible effect of SET8 miR-502 binding site SNP in terms of bladder cancer susceptibility. However, the findings for p53 codon 72 SNP revealed that CG genotype slightly increased the risk of bladder carcinoma compared to CC genotype. In regard to clinicopathological characteristics, no association was found for SET8 miR-502 binding site SNP though there was an association in terms of grade for p53 codon 72 SNP. In conclusion, the researchers findings reflect a partial protective effect of p53 CC (Pro/Pro) genotype against bladder cancer risk in Turkish population. However, there was no association between SET8 genotypes and bladder cancer risk stratification.

RECOMMENDATIONS

There are several studies in literature representing the associations/disassociations of the two selected SNPs in this study in terms of liability to several cancer types. Significantly different polymorphism distributions can be observed even in the same population inhabiting in different geographical locations and thus contributing to some discrepancies. The inconsistent outcomes may arise from different ethnic origins, environmental differences, and sometimes may be related to the complex genetic etiology of the disease. This study's relatively sufficient number of study group does not seem to be a main limitation. All the same, the researchers strongly recommend additional studies with larger sample sizes and different ethnicities to have a deeper insight on the effects of these two SNPs in bladder carcinoma.

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