Analysis of MNS16A VNTR polymorphic sequence variations of the TERT gene and associated risk for development of bladder cancer

Iqra Anwar a,b, Arshad A. Pandith a,c, Mohammad S. Wani d, Hyder Mir d, Meena Godha b, Aabid Koula, Zafar A. Shah e, Usma Manzoor e, Ina Amin e, Iqbal Qasim e

aAdvanced Centre for Human Genetics, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir, India; School of Life Sciences, Jaipur National University, Jaipur, Rajasthan, India; Department of Urology and Kidney Transplant, SKIMS, Srinagar, Jammu & Kashmir, India; dDepartment of Internal Medicine, SKIMS, Jammu & Kashmir, India; eImmunology and Molecular Medicine, SKIMS, Srinagar, Jammu & Kashmir, India

Abstract

Background: The MNS16A variable number tandem repeat (VNTR) polymorphism of the human telomerase reverse transcriptase (hTERT) gene acts as a regulator of hTERT promoter activity and has been shown to have a role in the predisposition toward various cancers. The current study aimed to investigate the association between MNS16A VNTR alleles and genetic predisposition to bladder cancer in the Kashmir region of northern India.

Materials and methods: A total of 130 patients with bladder cancer and 170 age- and gender-matched healthy controls were included in this study. Primer-specific polymerase chain reaction was used to genotype the different variants of VNTR alleles of the MNS16A VNTR polymorphism.

Results: Short allele VNTR-243 (SS) genotype frequency significantly differed between cases (9.23%) and controls (3.52%) (OR=3.08 [95% CI=1.10–8.61], p=0.042). The VNTR-243 short allele (S) was found significantly more frequent in bladder cancer cases (28.46%) than controls (20.88%) (OR=1.50 [95% CI=1.03–2.19], p=0.034). Likewise, the long allele (LL) hTERT MNS16A VNTR genotype was distributed more frequently in low stage disease versus high stage disease (60.29% vs. 39.70%) (OR=0.79 [95% CI=0.39–1.60], p=0.595).

Conclusion: The MNS16A VNTR short allele (S) was associated with a higher risk for bladder cancer in our population as compared to long alleles.

Keywords: Alleles; Bladder cancer; Kashmir; MNS16A VNTR; Polymerase chain reaction

1. Introduction

Bladder cancer, the most common malignancy of the urinary tract, is considered to be a diverse disease with different morphologic and clinical manifestations.[1] It is the 4th most prevalent malignancy and the 2nd most commonly diagnosed urologic cancer in men.[2] It is characterized by high rates of recurrence and poor prognosis, displaying an increase in incidence with increasing age.[3] The etiology of bladder cancer is multifactorial, with smoking known to be the most significant risk factor for development of bladder malignancy, while other risk factors include exposure to certain dyes, drugs, or arsenic, and certain chronic infections.[4] Genetic studies have identified a variety of genetic changes that occur during urothelial transformation that are associated with different clinical outcomes, including FGFR3, HRAS, NRAS activation in non-invasive bladder cancers and TP53, Rb1, E2F3 in muscle invasive bladder cancer.

The telomeres present at the ends of chromosomes help to maintain the integrity of the genomic structure.[5] The presence of a single stranded extension and protein complex with tandem nucleotide repeats of the hexamer TTAGGG in telomeres prevents chromosome degradation and stops fusions and rearrangements in eukaryotic chromosomes.[6–9] Human telomerase reverse transcriptase gene (hTERT), present in region 5p15.33, encodes a ribonucleoprotein enzyme that extends the chromosome ends which are shortened with each cell division.[10,11] It has been reported that control of telomerase action and telomere length is closely related to tumor formation in humans. Recent evidence suggests that genetic variation in the 5p15.33 region of the hTERT gene might play a role in regulating the risk of developing cancer.[10,11] Other evidence from genome-wide association studies (GWAS) has indicated the presence of a...
strong association between the locus at 5p15.33 and some cancers, including adenocarcinoma,[13] basal cell carcinoma, pancreatic cancer,[14] and lung cancer.[15,16] In addition, “risky” alleles present in this region have been reported to be significantly related to the occurrence of glioma,[17] bladder cancer,[18,19] and prostate cancer.[20] In terms of bladder cancer, activating certain genotypes or other related risk factors and bladder cancer. [21,24] bladder cancer,[26] and in colorectal cancer, [8,23] lung carcinoma, [22] nasal carcinoma, [22] colorectal cancer, [8,23] lung cancer,[21,24] prostate cancer,[23,25] and bladder cancer.[26] In this study, we aimed to determine whether the MNS16A VNTR polymorphism of the hTERT gene was associated with bladder cancer risk in a Kashmiri population.

2. Material and methods

2.1. Study population

The present study enrolled 130 patients with bladder cancer and 170 healthy controls (129 males and 41 females) who were free of any type of malignancy. Bladder cancer cases included 103 (79%) males and 27 (21%) females, a ratio of 4:1; 67% were smokers and 33% nonsmokers. Controls were matched to cases, and no gender, age, or smoking-related differences were observed between the 2 groups (p > 0.05). Subjects (cases and controls) were randomly recruited from the Department of Urology, SK Institute of Medical Sciences (SKIMS), Jammu & Kashmir, India, and were studied prospectively. All cases were selected after confirmation of transitional cell carcinoma by histopathological examination. This study was approved by the Ethics Committee of SK Institute of Medical Sciences, and written informed consent was obtained from all patients prior to participation in this study. Peripheral blood samples (5 mL) and corresponding tumor tissue samples were collected from Department of Urology and Kidney Transplant (SKIMS), and were preserved at −20°C for analysis.

2.2. Genotyping and allele confirmation

DNA was extracted from both peripheral blood and tumor tissues using the phenol-chloroform method and a DNA extraction kit (Zymo Research Corporation, USA). PCR was employed to amplify the genomic variants of the MNS16A VNTR polymorphism. For amplification of hTERT MNS16A, a 25 µL reagent solution was used containing genomic DNA: 250 ng/mL, 1× PCR buffer: 100 mM Tris–HCl, pH 8.3; 500 mM KCl; 15 mM MgCl₂; deoxyribonucleotide triphosphate (Biotools, B& M Labs, Madrid, Spain): 10 mM dATP; 10 mM dCTP; 10 mM dGTP; 10 mM dTTP, 10 pM primers (Sigma–Aldrich, USA); and Taq DNA polymerase 5 U/mL (Biotools, Madrid, Spain). The set of primers used for the MNS16A amplification encompassing the region with forward primer sequence was 5’-AGGATTCT- GATCTCTGAAGGTTG’-3’ (sense) and reverse primer was 5’-TCTGCTGGAGGACGATG’-3’ (antisense).[28] The PCR protocol was as follows; an initial denaturation at 95°C for 5 min, followed by denaturation for 35 cycles at 95°C for 30 s, and annealing at 60°C for 30 s, at 72°C for 1 min, and extension at 72°C for 10 min. The PCR products were further visualized on 3% high-resolution agarose gel under a UV transilluminator using Safe-T stained (ethidium bromide alternative).[16] The representative picture of hTERT MNS16A is shown in Supplementary Figure 1, http://links.lww.com/CURRUROL/A4. To ensure quality control, distilled water was used instead of DNA as a negative control.

2.3. Statistical analysis

Statistical analysis was done by using IBM Statistics SPSS software 23.0. Cases and controls were compared using the chi square test for categorical variables like gender and age demographic variables. A chi-square goodness-of-fit test was employed to evaluate whether the polymorphisms were in Hardy-Weinberg equilibrium between cases and controls. Odds ratios (OR) were used as estimates of relative risk, and 95% confidence intervals (CI) were calculated to estimate the association between certain genotypes or other related risk factors and bladder cancer. Statistical significance level was set at a p value < 0.05.

3. Results

In the present study, a total of 300 subjects (130 bladder cancer cases and 170 controls) were studied. Selected demographic characteristics of the case and control groups are demonstrated in Table 1. No significant difference was observed between groups in terms of gender, age or smoking (p > 0.05). The bladder cancer group consisted of 103 (79.23%) men and 27 (20.76%) women.

| Table 1 | Demographic characteristics of bladder cancer cases and healthy controls. |
|---------|-----------------------------|
| Variable | Cases (n = 130) | Controls (n = 170) | p  |
| Age, yr  |                  |                  |    |
| <50      | 46 (35.38%)       | 60 (35.29%)      | 0.920 |
| ≥50      | 84 (64.61%)       | 110 (64.70%)     |    |
| Gender   |                  |                  |    |
| Female   | 27 (20.76%)       | 41 (24.11%)      | 0.578 |
| Male     | 103 (79.23%)      | 129 (75.88%)     |    |
| Geographic area |           |                  |    |
| Rural    | 99 (76.15%)       | 112 (65.88%)     | 0.056 |
| Urban    | 31 (23.84%)       | 58 (34.11%)      |    |
| Smoking status |           |                  |    |
| Never    | 42 (32.30%)       | 73 (42.94%)      | 0.072 |
| Ever     | 88 (67.69%)       | 97 (57.05%)      |    |
| Histologic type |            |                  |    |
| G/G     | 72 (55.38%)       | 58 (44.61%)      |    |
| G/G 0.5 | 60 (45.38%)       | 82 (48.2%)       |    |
| Tumor stage |                  |                  |    |
| пTa/пT1 | 75 (56.99%)       | 80 (47.05%)      |    |
| пT2/higher | 55 (42.30%)     | 95 (55.29%)      |    |

www.cumurol.org
while the control group had 129 (75.88%) men and 41 (24.11%) women. There were 42 (32.30%) nonsmokers and 88 (67.70%) smokers in the bladder cancer group. Among bladder cancer cases, 75 (57.69%) had lower stage disease and 35 (42.30%) had higher stage disease; 72 (55.38%) had low grade disease and 58 (44.61%) had high grade disease. On stratification of bladder cancer cases, hTERT MNS16A LL genotype was more common in low grade cases (G-III/G-IV) as compared to high grade cases (G-II/G-IV), 55.88% versus 44.11%, respectively (OR = 0.95 [95% CI = 0.47–1.91], p = 1.00).

The observed genotype frequencies for the MNS16A variant were in Hardy-Weinberg equilibrium (HWE) with controls (p = 0.511). The results of genotyping are shown in Table 2, where different sizes of MNS16A (VNTR) alleles were analyzed and grouped as LL, LS, and SS on the basis of fragment size. Among these different sets of alleles, we found VNTR-302 (LL) allele to be the most common allele in both cases (71.53%) and controls (79.11%). On the other hand, the VNTR-333 allele was found at the lowest frequency. In our study, the genotype frequencies for 302/302, 333/302, 243/274, and 302/274, in our study only 333/302 was found in both cases and controls, 0.76% versus 1.17%, respectively. The short allele VNTR-243 (SS) genotype frequency was significantly different between cases and controls, at 9.23% versus 3.52%, respectively (OR = 3.08 [95% CI = 1.10–8.61], p = 0.042). Furthermore, distribution of the VNTR-243 allele was found to be significantly different between the 2 groups (28.46% in cases vs. 20.88% in controls) (OR = 1.50 [95% CI = 1.03–2.19], p = 0.034). No association was found between hTERT MNS16A genotype variation and gender or any other characteristic (Table 3). Likewise, hTERT MNS16A LL genotype was distributed more frequently in cases with low stage disease as compared to cases with high stage disease, 60.29% versus 39.70%, respectively (OR = 0.79 [95% CI = 0.39–1.60], p = 0.595). In addition, the frequency of combined genotype (LS+SS) was present more often in cases with both low grade and low stage disease (54.83%) compared to cases with both high grade and high stage disease (45.16%). We then performed Cox-Regression hazard analysis to determine whether the SS variant of hTERT MNS16A was independently associated with an increased risk of bladder carcinogenesis and not influenced by other variables. Multivariate analysis adjusted for physiological (age, gender, geographic area, smoking status, and pesticide exposure) and pathologic characteristics (disease grade and stage) confirmed that the hTERT-SS variant was an independent risk factor for bladder cancer; carriers

### Table 2
Genotypic/allelic distribution of hTERT MNS16A polymorphisms in bladder cancer cases and healthy controls.

| Parameter       | Cases (n=130) | Controls (n=170) | OR (95% CI) | p   |
|-----------------|---------------|------------------|-------------|-----|
| MNS16A          |               |                  |             |     |
| Long allele (LL)| 302           | 68 (52.30%)      | 105 (61.76%)| Reference |
| Short allele (LS)| 302/243      | 50 (38.46%)      | 59 (34.70%) | 1.30 (0.80–2.12) | 0.321 |
| L allele        | 302           | 12 (9.23%)       | 6 (3.52%)   | 3.08 (1.10–8.61) | 0.042 |
| S allele        | 243           | 186 (71.53%)     | 269 (79.11%)| Reference |
| Long short allele (LS) | 302/243  | 50 (38.46%)      | 59 (34.70%) | 1.30 (0.80–2.12) | 0.321 |
| Long allele (LL) | 302           | 68 (52.30%)      | 105 (61.76%)| Reference |

### Table 3
Genotypic distribution of hTERT MNS16A gene polymorphisms in bladder cancer cases and healthy controls with respect to different clinicopathological characteristics.

| Parameter       | Cases (n=130) | Controls (n=170) | Adjusted OR (95% CI) | p   |
|-----------------|---------------|------------------|----------------------|-----|
| Overall genotype |               |                  |                      |     |
| Age, yr         |               |                  |                      |     |
| <50             | 46 (35.38%)   | 23 (33.82%)      | 23 (37.09%)          | 60 (35.29%) | 1.47 (0.92–2.33) | 0.125 |
| ≥50             | 84 (64.61%)   | 45 (66.17%)      | 39 (62.90%)          | 110 (64.7%) | 1.85 (1.03–3.34) | 0.052 |
| Sex             |               |                  |                      |     |
| Male            | 103 (79.23%)  | 55 (80.88%)      | 48 (77.41%)          | 129 (75.8%) | 1.25 (0.74–2.11) | 0.425 |
| Female          | 27 (20.76%)   | 13 (19.11%)      | 14 (22.58%)          | 41 (24.11%) | 2.60 (0.94–7.15) | 0.077 |
| Smoking status  |               |                  |                      |     |
| Never           | 42 (32.30%)   | 23 (33.82%)      | 19 (30.64%)          | 97 (57.05%) | 1.25 (0.58–2.70) | 0.694 |
| Ever            | 88 (67.69%)   | 45 (66.17%)      | 43 (69.35%)          | 61 (35.09%) | 1.61 (0.90–2.91) | 0.136 |
| Geographic area |               |                  |                      |     |
| Rural           | 99 (76.15%)   | 49 (72.05%)      | 50 (80.64%)          | 112 (65.8%) | 1.76 (1.01–3.06) | 0.051 |
| Urban           | 31 (23.85%)   | 19 (27.94%)      | 12 (19.35%)          | 58 (34.11%) | 0.89 (0.36–2.18) | 0.825 |
| Histologic type |               |                  |                      |     |
| G3G3            | 72 (55.38%)   | 38 (55.86%)      | 34 (54.83%)          | 34 (53.84%) | 0.95 (0.47–1.91) | 1.00  |
| G3G1/G1G1       | 58 (44.61%)   | 30 (44.11%)      | 28 (45.16%)          | 34 (53.84%) | 0.79 (0.39–1.60) | 0.595 |
| Tumor stage     |               |                  |                      |     |
| pTaG/pT1        | 75 (57.69%)   | 41 (60.20%)      | 34 (54.83%)          | 34 (53.84%) | 0.79 (0.39–1.60) | 0.595 |
| pTaG/pT2        | 55 (42.30%)   | 27 (39.70%)      | 28 (45.16%)          | 34 (53.84%) | 0.79 (0.39–1.60) | 0.595 |

LL = long allele; LS = long short allele; SS = short allele; CI = confidential interval; OR = odds ratio.
of this variant had increased risk of developing bladder cancer more than 3 times higher than that of non-carriers (HR = 3.34, p = 0.04) (Supplementary Table 1, http://links.lww.com/CURRUROL/A3).

4. Discussion

Currently, increased telomerase activity is regarded as a prominent risk factor for different types of cancer that plays a vital role in their growth and progression. Various studies have investigated functional polymorphic variations impacting the expression or function of the hTERT gene which increase susceptibility for bladder cancer. The association between MNS16A VNTR and different cancers, including breast, glioblastoma multiforme, and non-small cell lung cancer, has been investigated with variable findings with respect to unique VNTRs depending on their lengths.

In the present study, the impact of hTERT variants on bladder cancer risk was analyzed in one ethnic population of the Kashmir region of northern India. The current study found a significantly increased frequency, around 3-fold higher, of the short allele VNTR-243 (SS) genotype in cases as compared to controls (9.23% vs. 3.52% respectively) (p = 0.042). This finding supports the hypothesis that VNTR-243 (SS) confers an increased risk for bladder cancer.

A previous study investigating lung cancer confirmed that hTERT mRNA expression is regulated by MNS16A. Additionally, VNTR-SS allele was significantly associated as a risk factor for colorectal cancer compared with the VNTR-302 wild-type by Hofer et al. Yan Wang et al also found that the SS genotype (243/243) of MNS16A in Chinese women with breast cancer was significantly related with an increased risk of breast cancer. Another study in a non-Hispanic white population found the VNTR-243S allele to be significantly more frequent in glioma cases (28.46%) than controls (20.88%) (p = 0.034). Furthermore, a study on lung cancer with respect to MNS16A polymorphic analysis included a large number of samples, with 937 patients and 943 healthy controls. This study showed the SS form of VNTR-243 was associated with an elevated risk of lung cancer. On the contrary, despite the fact that MNS16A polymorphic variation has been studied in numerous contexts related to a number of different cancers results are conflicting, either due to ethnic variations or some other technical reasons. For example, a study conducted in China found no significant differences between MNS16A polymorphisms among pericentenarian and normal controls. Another study on MNS16A polymorphisms in prostate cancer cases and controls with benign prostatic hyperplasia showed no significant association with any variant form. In a study on bladder cancer, Songül Diler et al found comparable distributions of MNS16A VNTR SS/alleles and SS/LL genotypes among bladder cancer cases and controls with no significant differences. Nonetheless, one common finding in our study and their study was a similar frequency of MNS16A SS genotype, 9.2% versus 10%, respectively.

In sum, given the plausible role of the S allele of MNS16A to confer risk for different cancers, as demonstrated in the current study and relevant studies noted above, this allele shows promise as a potential relevant tumor risk marker. This is further supported by the finding that the MNS16A S allele is linked with enhanced hTERT expression, which signifies that MNS16A genetic variation is a potential factor that affects hTERT mRNA expression and therefore influences the risk for various cancers, in particular bladder cancer. No single clinical or pathological parameter such as smoking status, histological type, tumor stage, or geographic area were found to be associated with different genotypes of MNS16A (p > 0.5), although age < 50 years approached statistical significance (p = 0.052). These results are consistent with other studies on breast cancer conducted by Hashemi et al and bladder cancer conducted by Diler et al where all clinical and pathological parameters showed no association.

It is known that genetic polymorphic variations demonstrate variable prevalences in different ethnic groups. The frequency of MNS16A in the current study showed similarities and discrepancies with other ethnic populations, as depicted in Table 4. The

| Author            | Year | Cancer type | Cases | Controls |
|-------------------|------|-------------|-------|----------|
| Songül Diler      | 2020 | Bladder     | 29    | 47       |
| Luo Wang          | 2003 | Lung        | 30    | 33       |
| Philip Herbst     | 2011 | CRC         | 115   | 135      |
| Hashemi           | 2014 | Breast      | 133   | 120      |
| Luo Wang          | 2006 | GBM         | 133   | 106      |
| Yan Wang          | 2008 | Breast      | 860   | 984      |
| Yang Zhang        | 2011 | NPC         | 725   | 891      |
| Martinson         | 2016 | Renal cell  | 116   | 148      |
| Wysoczanska       | 2015 | Lymphoma    | 28    | 53       |
| Zagouri           | 2015 | Breast      | 50    | 83       |
| Jin               | 2011 | Lung        | 820   | 840      |
| Andersonson       | 2009 | Gloma       | 282   | 650      |
| Carpenter         | 2007 | Gloma       | 126   | 133      |
| Current study     | 2020 | Bladder     | 68    | 105      |

**Note:** CRC = colorectal cancer; GBM = Glioblastoma; NPC = nasopharyngeal cancer; LL = long allele; LS = long short allele; SS = short allele.

Table 4 Comparison of various studies regarding hTERT MNS16A polymorphisms.
frequencies of different alleles of MNS16A observed for cases in our population correlated most closely with studies conducted on different cancers in Caucasian populations[25,32,33] and ethnic groups of Turkish descent.[26] Although the frequency of different alleles in our control group correlated closely with those reported by Martino et al,[33] the overall distribution varied considerably across all included studies (Table 4).[8,16,21,26,28,29,31–36] This shows considerable variation in MNS16A alleles among different ethnic populations and makes it an interesting genetic polymorphism to be investigated as a risk factor for different cancers.

5. Conclusion
This study found that both MNS16A VNTR short allele (S) and genotype (SS) are associated with an increased risk for bladder cancer in our study population as compared to long alleles. These findings need to be replicated in more studies on urinary tract cancers.

Acknowledgments
Authors thank Department of Urology for their help to procure the bladder cancer samples and keep record of the patients. We also thank and acknowledge the bladder cancer patients for their cooperation.

Statement of ethics
This study was approved by the Ethics Committee of SK Institute of Medical Sciences, and written informed consent was obtained from all patients prior to participation in this study. All procedures involving human subjects were conducted in compliance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest statement
The authors declare no conflicts of interest.

Funding source
None.

Author contributions
Arshad A. Pandith: Design of the study, conception of and writing the draft manuscript and figures;
Iqra Anwar: Data interpretation, conducting experiments, statistical analysis;
Mohammad S. Wani: Provided samples, revisions to the draft manuscript;
Usma Manzoor, Ina Amin, Hyder Mir, Aabid Koul, Meena Godha, Iqbal Qasim, Zafar A. Shah: Assisted in conducting experiments.
Iqra Anwar and Arshad A. Pandith contributed equally.

Data availability
All data that support the results and conclusions of this manuscript will be made accessible to any eligible researcher.

References
[1] Boswick DG, Cheng L. Urologic Surgical Pathology. 3rd ed. Philadelphia: Elsevier/Saunders; 2014.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30.
[3] Sanli O, Dobruch J, Knowles MA. Bladder cancer. Nat Rev Dis Primers 2017;3:17022.
[4] Babyk M, Bohle A, Burger M, et al. EAU Guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2016. Eur Urol 2017;71(3):447–461.
[5] Moon I, Jarstfer M. The human telomere and its relationship to human disease, therapy, and tissue engineering. Front Biosci 2007;12:4595–520.
[6] Mirabelli L, Yu K, Kraft P, et al. The association of telomere length and genetic variation in telomere biology genes. Hum Mutat 2010;31(9):1050–1058.
[7] Tsuchiya T, Sawabe M, Takubo K, et al. hTERT promoter polymorphism, −1327C>T, is associated with the risk of epithelial cancer. Springerplus 2013;2(1):249.
[8] Hofer P, Baierl A, Feik E, et al. MNS16A tandem repeats minisatellite of human telomerase gene: A risk factor for colorectal cancer. Carcinogenesis 2011;32(6):866–871.
[9] Liu L, Wang C, Lu X, et al. The MNS16A polymorphism in the TERT gene in peri-centenarians from the Han Chinese population. Sci China Life Sci 2014;57(10):1024–1027.
[10] Baird D. Variation at the TERT locus and predisposition for cancer. Expert Rev Mol Med 2010;12:e16.
[11] Engellhardt M, Albanell J, Drulhinsky P, et al. Relative contribution of normal and neoplastic cells determines telomerase activity and telomere length in primary cancers of the prostate, colon, and sarcoma. Clin Cancer Res 1997;3(10):1849–1857.
[12] Pande M, Spitz MR, Wu X, Gorlov IP, Chen WV, Amos CI. Novel genetic variants in the chromosome 5p15.33 region associate with lung cancer risk. Carcinogenesis 2011;32(10):1493–1499.
[13] Jin G, Xu L, Shu Y, et al. Common genetic variants on 5p15.33 contribute to risk of lung adenocarcinoma in a Chinese population. Carcinogenesis 2009;30(6):987–990.
[14] Petersen K, Amundsdotter L, Fuchs C, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet 2010;42(3):224–228.
[15] McKay JD, Hung RJ, Gaborieau V, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet 2008;40(12):1404–1406.
[16] Jin G, Yoo SS, Cho S, et al. Dual roles of a variable number of tandem repeat polymorphism in the TERT gene in lung cancer. Cancer Sci 2011;102(1):144–149.
[17] Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet 2009;41(8):899–904.
[18] Rachakonda PS, Hosen I, de Verdier PJ, et al. TERT promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci U S A 2013;110(43):17426–17431.
[19] Giedl J, Rogler A, Wild C, et al. TERT core promoter mutations in early-onset bladder cancer. J Cancer 2016;7(8):915–920.
[20] Shadrina AS, Boyarskikh UA, Oskina NA, et al. TERT polymorphisms rs2853669 and rs7726215 influence on prostate cancer risk in Russian population. Tumour Biol 2013;34(2):841–847.
[21] Wang L, Soria JC, Chang YS, Lee HY, Wei Q, Mao L. Association of a functional tandem repeats in the downstream of human telomerase gene and lung cancer. Oncogene 2003;22(46):7123–7129.
[22] Zhang Y, Zhang H, Zhai Y, et al. A functional tandem-repeats polymorphism in the downstream of TERT is associated with the risk of nasopharyngeal carcinoma in Chinese population. BMC Med 2011;9:106.
[23] Hofer P, Zochmeister C, Behm C, et al. MNS16A tandem repeat minisatellite of human telomerase gene: Functional studies in colorectal, lung and prostate cancer. Oncotarget 2017;8(17):28021–28027.
[24] Wang L, Wang LE, Mao L, Spitz MR, Wei Q. A functional variant of tandem repeats in human telomerase gene was associated with survival of patients with early stages of non-small cell lung cancer. Clin Cancer Res 2010;16(14):3779–3785.
[25] Hofer P, Zerelles J, Baierl A, et al. MNS16A tandem repeat minisatellite of human telomerase gene and prostate cancer susceptibility. Mutagenesis 2013;28(3):301–306.
