# Genetic Association between Human Telomerase-associated Protein 1 Polymorphism with Bladder Cancer Risk and Staging

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**Abstract**

Telomerase-associated protein 1 is responsible ribonucleoprotein complex for telomerase activity, which catalyzes new telomeres on the chromosome ends. The presented work studied the impact of (TEP1) single nucleotide polymorphism on bladder CA risk. A total of sixty-two diagnosed by histo-pathologically with Transitional cell carcinoma (TCC) individuals and thirty-eight individuals as controls were implicated in the research. TEP1 rs222804 Polymorphism (C>T) was estimated by amplifying the gene with PCR and DNA sequencing methods. This study revealed that the polymorphic T allele related to TEP1 rs222804 Polymorphism has a considerable association in increase TCC risk with an odds ratio of 4.7. Also, a significant association has been observed between T allele and increasing TCC risk among smoker individuals 7.02 (1.48-33.25), p=0.01. Furthermore, the T allele showed a significant association for the T2 stage of TCC (OR=13.2, 95 % CI=2.7-64.1), p=0.001. This data leads to suggestions that the TEP1 rs222804 genotype could be involved in increasing TCC risk.

***Keywords:*** *Telomerase-associated Protein1, chromosome, Transitional cell carcinoma, Polymorphism, complex.*

# العلاقة الجينية لبروتين 1 المرتبط بالتيلوميريز متعدد الأشكال البشري وخطورة زيادة الإصابة بسرطان المثانة

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**الخلاصة**

البروتين 1 المرتبط بالتيلوميريز هو مركب نيكولوبروتيني مسؤول عن نشاط التيلوميريز ، والذي يحفز تكوين تيلومير جديد على نهايات الكروموسوم. في هذا البحث تم دراسة تأثير تعدد أشكال النوكليوتيدات المفردة لجين البروتين 1 المرتبط بالتيلوميريز على زيادة نسبة الاصابة بسرطان المثانة وقد شارك في البحث مجموعتان الاولى مكونة من اثنان وستون



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شخصًا تم تشخيصهم بسرطان الخلايا الانتقالية وثمانية وثلاثين فردًا من الاشخاص السليمين تم استخدامهم كنماذج سيطرة. وقد تم الكشف عن الطفرة المسجلة rs222804 لجين البروتين 1 المرتبط بالتيلوميريز متعدد الأشكال (T <C) عن طريق تضخيم الجين باستخدام تفاعل البلمرة المتسلسل وتحديد تتابع الحمض النووي. وقد كشفت هذه الدراسة أن الأليل T ذو الطفرة المسجلة rs222804 لجين البروتين 1 المرتبط بالتيلوميريز متعدد الأشكال (T <C) الأشكال له ارتباط كبير في زيادة مخاطر سرطانة الخلايا الانتقالية مع نسبة أرجحية 4.7. أيضًا ، كمت وقد لوحظ ارتباط كبير بين T allele وزيادة خطر سرطانة الخلايا الانتقالية بين الأفراد المدخنين 7.02 (1.48-33.25) ، p = 0.01. علاوة على ذلك ، أظهر أليل T ارتباطًا مهمًا بمرحلة الثانية من سرطان الخلايا الانتقالية من TCC (OR = 13.2، 95٪ CI = 2.7-64.1)، p = 0.001. تؤدي هذه البيانات إلى اقتراحات بأن النمط الجيني ذو الطفرة المسجلة rs222804 لجين البروتين 1 المرتبط بالتيلوميريز متعدد الأشكال (T <C) يمكن أن يشارك في زيادة مخاطر سرطانة الخلايا الانتقالية .

***الكلمات المفتاحية:*** *بروتين 1 المرتبط بالتيلوميريز, كروموسوم, سرطانة الخلايا الانتقالية , تعدد الاشكال , معقد .*

## 1.Introduction

Telomerase, is responsible for lengthening and maintaining telomeres, also it comprises of the telomerase RNA component (TERC) and Telomerase reverse transcriptase (TERT), the catalytic element [1]. The use of the TERC as a template for TERT, which maintains the length of the telomere, facilitates the synthesizing of new "TTAGGG" DNA repeats. Hematopoietic progenitor cells, germ cells, activated lymphocytes, and the majority of cancer cells have high telomerase activity, which prevents telomere shortening and allows for unrestricted cell division and replication [2]. Telomerase activity has lately been discovered in a variety of tumor cancers, including prostate cancer, lung cancer, TCC and breast cancer [3-6]. So, it necessary to understand the mechanism and this association with these cancers. The catalytic subunit of telomerase (hTERT) has many associated proteins (TEP1 P23/p90) [7]. Previous studies on TEP1 polymorphisms were reported in many cancers like ovarian cancer, prostate cancer, and breast cancer [8-10]. A very recent study showed a significant association between TEP1 Polymorphism and TCC [11].

Also, rs222804 is one of the TEP1 polymorphisms and could be associated with TCC risk. TEP1 rs222804 polymorphism is considered as non-synonymous SNP that changing arginine to glutamine at position 1155 in the protein. Changing a highly basic amino acid to a neutral amino acid can have a significant impact on protein structure and function [12]. Yet, more research is needed to see how such TEP1 SNP impacts TEP1 function, telomerase activity, and the risk of TCC in the future. Different vocational and ecological factors, including carcinogens and biochemicals, including aromatic hydrocarbons, aromatic amines, ROS, and other anticancer drugs, have been found to increase the incidence of TCC in previous studies [13]. On the other hand, exposure to these factors can vary in the developing TCC. That is leading to the suggestion of gene-occupational



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associated with bladder cancer risk [14]. Elevated TCC risk factors were seen as tobacco smoking. There are carcinogenic chemicals existing in the citrate as naturally or can be generated during ignition of the citrate; both of them can be induced tumor-forming [15]. Also, during multistage lung carcinogenesis, telomerase showed an increase in its expression [16,17]. A similar increase was noticed in normal bronchial mucosa and precancerous lesions of heavy smokers [18], suggesting that tobacco smoking could have a role in telomerase reactivation. In immortalized bronchial epithelial cells of smokers in comparison to non-smokers, an increase in telomerase activity was found, with a significant connection with the number of packs years [19]. Also, telomere length was assessed as a functionally linked end-point and potential biomarker of smoke-related oxidative stress at the same time [16]. Telomere DNA is very susceptible to oxidative damage due to its high guanine concentration, and oxidative stress is a primary predictor of telomere erosion[20,21]. Cigarette smoke has been shown to modify the DNA methylation profile of blood cells[22-27], and telomerase activity can be influenced by epigenetic modifications to its catalytic subunit (hTERT) [28]. Furthermore, the methylation status regarding *hTERT* gene was investigated to see if there was a link between telomerase activity and *hTERT* epigenetic modifications [16].

The relation of TEP1 rs222804 single nucleotide polymorphisms and cigarette smoking impact on TCC risk is not fully discovered. In this study, it has been suggested that the association between tobacco smoking and rs222804 genotype may involve in increasing TCC and affect its staging. To Evaluate this hypothesis; it has been genotyped TEP1 rs222804 polymorphisms in case-control study of TCC patients in Baghdad city.

## 2. Materials and methods

### 2.1. Collection of samples

This study was submitted to Baghdad university/college of medicine/chemistry department. A case-control researcher was carried out on one hundred individuals from January 2019 to October 2019. All subjects were taken from the hospital of Gazi Al-Harery for Specialized Surgery. One hundred individuals, sixty-two individuals (forty-seven males, fifteen females) with transitional cell carcinoma, and thirty-eight (twenty-eight males, ten female) cancer-free subjects. The issue involves in this research were a match in sex and age. All patient participants were diagnosed, and histopathology was confirmed with a tumor of the bladder tumor. The significant criteria excluded from the study were as follows: individuals with a urinary tract infection history, previous cancer patients, metastasized to the bladder from another origin, chemotherapy, and radiotherapy patients.



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Individuals who are taken as controls in this study were free from any type of cancer and had no history of tumors. In this study, we assumed the individual that smoke once a day and for a period of more than a year ever-smoker. After taking the residents' agreement and authorization. The work's samples have been taken as whole blood samples, which were placed in EDTA sterile tubes and stored at a temperature of -4°C for DNA extraction.

**2.2. Genotyping and DNA Extracting**

The human DNA has been obtained from the entire blood that has been collected in 5.0ml tubes, including ethylene-diamine-tetra acetic acid (K3EDTA) from patients with TCC and free-cancer controls, using a Promega DNA extraction kit. For additional SNP genotyping, the extracted DNA was frozen at a temperature of 80°C. PCR was used to amplify TEP1 rs222804 fragments. Primers for genotyping of TEP1 rs222804 gene Fragments were. The primer sequences have been newly designed 5′- GACCCATTTACCCTCAGCCT -3′ (reverse) and 5′- GCCTTACCTCCTTAGCCCAC -3′ (forward). The fragments related to TEP1 rs222804 polymorphism have been amplified in 25 mL of reaction mixture which contains two micro litter of the template of genomic DNA, 0.75µl of every one of the primers, nine micro litter of free nuclease water from Promega, 12.50µl of the PCR master mixture (Promega, US), containing 0.10mM of every dNTP, a PCR buffer, ten millimoles 50 mM KCl Tris-HCl, and 1.5mM $MgCl_2$ (0.10%Triton X-100), and 1 Taq polymerase unit.

The amplification of the PCR has been set up as: 1 cycle at 95 Celsius for 4mins as a step of denaturation; 30 cycles at 95$^o$ Celsius for 30sec, 60$^o$ Celsius for 30sec, and 72$^o$ Celsius for 30sec; and a final extension at 72$^o$ Celsius for 7 mins. Figure 1 shows a 275-bp PCR result that was verified on a 2% agarose gel. Additionally, all PCR products were submitted to South Korea for the direct sequencing utilizing Sanger sequencing approach. As indicated in Figure (2), the software "genious" was used to analyze the sequencing findings.



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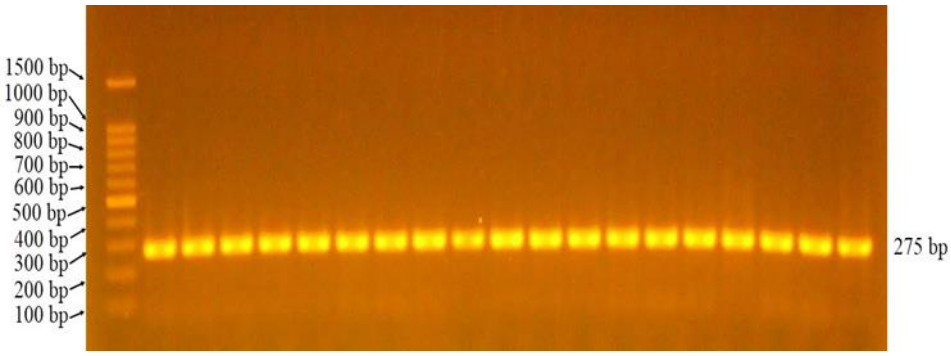


**Fig. (1)**: Electrophoretic graph of PCR product of TEP1 rs2228041 Gene polymorphism with the use of the Promega master mixture on high-resolution agarose 2 %, 70 V, and for two hours (7µl of DNA that has been loaded in every one of the wells)

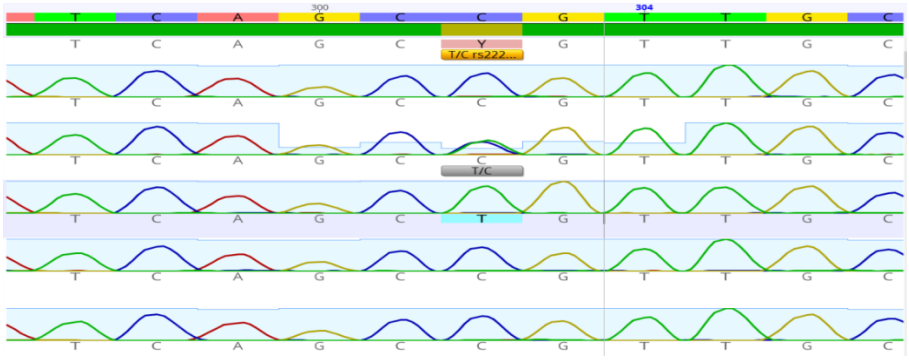

**Fig. (2)** Sequencing analyses by "genious" program for TEP1 rs2228041 Polymorphism

following the sequencing by the Sanger sequencing, automated DNA sequencer, by the Macro-gen Co. – Korea. This figure shows various types of TEP1 rs2228041 Polymorphism every line of the sequencing represents diverse individual sample 3 Sequencing line had shown:

- T/C genotype as a blue and green band (i.e. heterozygous)
- CC genotype as a single blue band (i.e. wild type)
- TT genotype as a single blue-green band (i.e. homopolymeric).

### 2.3. Statistical analyses

Google spreadsheet was used in this study to store the data and were analyzed by SPSS software. Stander deviation and the mean were used to express the numeric variable and showed (mean ± SD). The comparison of the mean between the 2 groups was analyzed with the use of student t-test. Comparing the frequency was made using Chi-square for assessing the differences in frequency distributions of individual variables and demographic characteristics.



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Also, Chi-square was used to evaluate the difference between Transitional cell carcinoma cases and the control group in TEP1/rs228041 polymorphism allele genotype. Multivariate logistic regression and unconditional univariates have been used in order to obtain the association of genetic /rs2228041 on the Transitional cell carcinoma risk and the combined tobacco effect on Transitional cell carcinoma staging.

## 3. Results

### 3.1. Characteristic of the subjects

In this case-control study, a total of one hundred individuals were analyzed. Thirty-eight healthy subjects were used as a control group compared to sixty-two Transitional cell carcinoma patients (table 1 and table 2). In this controlled study, age, BMI, sex, weight, Hight, and showed as Mean ± SD. The healthy control group means a ge was 63±6.5 years, while 63±8.3 were calculated for Transitional cell carcinoma patients. The absence of differences in these factors makes it excluded from affecting the results of polymorphism when comparing the patient group with the control group.(Transitional cell carcinoma and control) for these parameters p-value more than 0.05.

**Table (1):** study demographic characteristics.

| Category | Cases n=68 (mean ± SD) | Controls n=38 (mean ± SD) | *P* |
|---|---|---|---|
| Age | 63.6±8.3 | 63±6.5 | 0.38 |
| weight | 80.5±10.3 | 82.4±11.2 | 0.09 |
| Height | 170.7±9.5 | 167.9±6.9 | 0.07 |
| BMI | 27.8±4.2 | 29.3±3.9 | 0.06 |

In this study, the males showed a higher risk of having TCC, the female, and established in table 2. It has been found that subjects with the age of (60) years have the highest risk of Transitional cell carcinoma than other age groups, which is shown in table 2. Transitional cell carcinoma risk increased with tobacco smoking individuals compared to the non-tobacco smoking group; p-value was 0.03. In this paper, the association of TEP1/rs228041 Polymorphism with the staging of Transitional cell carcinoma were made by grouping the patients into three groups ((Ta, T1, T2) and higher frequency stage was found in the T1 group N%= (41.9%) as shown in table2.



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**Table (2):** Distributions of the frequency of selected variables between the Transitional cell carcinoma cases and cancer-free controls

| Variable | | Cases (n = 62) | | Controls (n = 38) | | | |
|---|---|---|---|---|---|---|---|
| | | Count | N% | Count | N% | OR (95% CI) | *p*† |
| Sex | Female | 15 | 24.20 % | 10 | 26.30% | 1 | - |
| | Male | 47 | 75.80 % | 28 | 73.70% | 1.11 (0.44-2.82) | 0.81 |
| | | | | | | | |
| Age group (years) | >60 | 39 | 62.9% | 26 | 68.4% | 1.00 | - |
| | <=60 | 23 | 37.1% | 12 | 31.6% | 1.2 (0.54-3.00) | 0.57 |
| | | | | | | | |
| Smoking status | Never-Smoker | 19 | 30.60 % | 20 | 52.60% | 1 | - |
| | Ever-Smoker | 43 | 69.40 % | 18 | 47.40% | 2.51 (1.09-5.79) | 0.03* |
| | | | | | | | |
| Cancer Stage | Ta | 17 | 27.4% | - | - | - | - |
| | T1 | 26 | 41.9% | - | - | - | - |
| | T2 | 19 | 30.6% | - | - | - | - |

### 3.2. Genotypes and Allele frequencies for TEP1/ rs2228041 Polymorphism

The distribution of rs2228041 genotyping of TEP1 in 68 Transitional cell carcinoma patients and 38 cancer-free controls was done using Hardy– Weinberg equilibrium shown in table 3. In both TCC patients and cancer-free controls, CC genotype (79.03% and 94.73%, respectively) was significantly higher (p-value >0.05) than CT (19.35% and 5.26%, respectively) and TT (1.61% and 0%, respectively) genotypes. Wild-type p-allele was higher than the wild q type both Transitional cell carcinoma patients and control group. Thus, C allele was 0.89 in the TCC patients and 0.97 in the control group,whereas the T allele was 0.11 in the TCC patients and 0.03 in the control group.

**Table (3):** Genotypes and Allele frequencies of TEP1/ rs2228041 amongst theTransitional cell carcinoma and control.

| TEP1/ rs2228041 C/T | Genotypes, n (%) | | | Allele frequencies | | (HWE) *p-value* |
|---|---|---|---|---|---|---|
| | **CC** | **CT** | **TT** | **P** | **Q** | |
| Transitional cell carcinoma | 49 (79.03) | 12 (19.35) | 1 (1.61) | 0.89 | 0.11 | 0.79 |
| Control | 36 (94.73) | 2 (5.26) | 0 (0) | 0.97 | 0.03 | 0.86 |



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### 3.3. Comparison of TEP1/ rs2228041 polymorphism

As indicated in table 4, odds ratios for TEP1/ rs2228041 were determined by comparing the heterozygous wild type (CC) to the other genotypes (homozygous polymorphic genotype TT genotype, heteroz ygous CT genotype, and CT+TT). Individuals caring for the TT genotype show no significantly high Transitional cell carcinoma risk with OR of 2.21 (0.08-55.8), *p*=0.6. Also, no significant relation has been identified in study subjects that carried CT genotype. However, a high, significantly, Transitional cell carcinoma risk was observed when comparing CT+TT genotype and taking the CC genotype as a reference with an OR of 4.7 and a p-value of 0.04.

The polymorphic T allele effect was measured with an Odd Ratio by taking the whole T allele in the study individual against the wild-type G allele genotype. The T allele frequencies in a total Transitional cell carcinoma individual were approximately five-fold higher compared controls, and its difference was significant as well (p=0.04), as shown in table 4.

**Table (4):** Distribution/genotyping of TEP1/ rs2228041 polymorphisms in 68 Transitional cell carcinoma patients and 38 controls without cancer.

| | **Case (n = 68)** | | **Control (n = 38)** | | | |
|---|---|---|---|---|---|---|
| TEP1/ rs2228041 | **Counts** | **N %** | **Counts** | **N %** | **OR (95% CI)** | **p** |
| CC | 49 | 79.0% | 36 | 94.7% | 1.00 | - |
| CT | 12 | 19.4% | 2 | 5.3% | 4.4 (0.92-20.9) | 0.06 |
| TT | 1 | 1.6% | 0 | 0.0% | 2.21 (0.08-55.8) | 0.6 |
| CT+TT | 13 | 21.0% | 2 | 5.3% | 4.77 (1.0-22.4) | 0.04* |
| C | 110 | 88.7% | 74 | 97.3% | 1.00 | - |
| T | 14 | 11.3% | 2 | 2.65% | 4.7 (1.0-21.3) | 0.04* |

### 3.4 Association of TEP1/ rs2228041 Polymorphism with status of the smoking

Combined impact of TEP1/ rs2228041 polymorphisms and smoking is shown in table 5. For measuring the combined impact of TEP1/ rs2228041 Polymorphism with smoking status, the wild-type allele genotypes in non-smoker individuals has been taken as a reference genotype. A non-significant Transitional cell carcinoma risk (OR = 0.12-82.01) in non-smokers who carried T allele. However, both C and T smoker individuals showed significant high Transitional cell carcinoma risk with a p-value less than 0.05. Smoking and have the C allele showed a significant Transitional cell carcinoma risk with an OR of 2.23, while smoking and having polymorphic T allele had shown a higher significant bladder risks with an OR of 7.02, which is shown in table 5.



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**Table (5):** Impacts of Smoking on TEP1/ rs2228041 Allele polymorphism in the cases and the controls.

| Smoking status | Genotypes | Counts | n % | Counts | n % | OR (95% CI) | p |
|---|---|---|---|---|---|---|---|
| Non-smokers | C | 37 | 48.7% | 40 | 50.0% | 1.00 | - |
| | T | 1 | 1.3% | 0 | 0.0% | 3.2 (0.12-82.01) | 0.47 |
| Smokers | C | 73 | 42.4% | 34 | 47.2% | 2.23 (1.26-4.24) | 0.01* |
| | T | 13 | 7.6% | 2 | 2.8% | 7.02 (1.48-33.25) | 0.01* |

### 3.5 Association between TEP1/ rs2228041 Genotype and Transitional Cell Carcinoma Stage

Depending on the stage of TCC, patients have been split into 3 groups (low stage Ta, medium T1, higher stage T2). When three-stage genotypes were compared to the control genotypes, the odds ratio was calculated. As indicated in table 5, wild-type CC genotype has been used as a reference and compared to CT+TT genotype. There was no significant association of TEP1/ rs2228041 genotypes for the Ta and T1 (P = (0.4, 0.69)) respectively. The TT+CT genotype of the TEP1/ rs2228041 showed increased risk with the T2 Transitional cell carcinoma stage (OR=16.2, 95 % CI= 3.0-87.3). A Similar statically significant risk has been observed in the T polymorphic allele in the case of taking the C wild-type allele as a reference; the p-value for the T2 was 0.001 (OR=13.2, 95 % CI=2.7-64.1).

**Table (6):** Associations of TEP1/ rs2228041 polymorphism with the categories of the tumor stages

| | Control N(%) | Transitional cell carcinoma Stage N (%) | | | (a-b) | | | (a-c) | | | (a-d) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TEP1/ rs2228041 | (a) | Ta(b) | T1(c) | T2+(d) | OR | 95 % CI | P | OR | 95 % CI | P | OR | 95 % CI | p |
| CC | 36 (94.7) | 15 (88.2) | 24 (92.3) | 10 (52.6) | 1.00 | | | | | | | | |
| CT+TT | 2 (5.3) | 2 (11.8) | 2 (7.7) | 9 (47.4) | 2.4 | 0.30-18.6 | 0.4 | 1.5 | 0.19-11.3 | 0.69 | 16.2 | 3.0-87.3 | 0.001** |
| C | 74 (97.4) | 32 (94.1) | 50 (96.2) | 28 (73.7) | 1.00 | | | | | | | | |
| T | 2 (2.6) | 2 (5.9) | 2 (3.8) | 10 (26.3) | 2.31 | 0.31-17.1 | 0.41 | 1.48 | 0.2-10.8 | 0.69 | 13.2 | 2.7-64.1 | 0.001** |



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## 4. Discussion

Telomerase-Associated Proteins (TEP1) is an enzyme that has an essential function in the elongation of telomeres. In the current study, an SNP in the TEP1 protein with reference SNP of rs2228041 has been analyzed, and its risks to Transitional cell carcinoma were Investigated. In the present study, the polymorphic allele frequency of TEP1 rs2228041 Polymorphism in 68 Transitional cell carcinoma individuals was 0.11 and higher than the control group 0.03. Moreover, both control and Transitional cell carcinoma patients were no deviation from Hardy– Weinberg equilibrium p-value >0.05, recommended in such studies [29]. A previous study was analyzed rs2228041 Polymorphism in Caucasian patients. However, their polymorphic allele frequency for this Polymorphism is much lower than the current research (q allele freq = 0.04) [12]. This Polymorphism Changes Arginine to Glutamine at codon 1155, and this change could affect the activity of enzymes and shorten the telomere, leading to many cancers [30]. An association of the rs2228041 Polymorphism and Transitional cell carcinoma was observed in the individual who carries the polymorphic T allele (p=0.04). T allele was noticed to highly significantly increased Transitional cell carcinoma risk with an OR of 4.7. Similar results were observed with ovarian cancer (OR= 2.11, p=0.0070) [30]. Moreover, Telomerase-Associated Proteins SNPs have been related to many cancer risks, including stomach cancer [31], breast cancer [31], prostatic cancer [33], and the risk of type 2 diabetes [34]. However, there was no association with increased Transitional cell carcinoma risk for TT genotype of the TEP1 rs2228041 Polymorphism, but there was a highly significant increase when comparing the two genotypes (CT+TT) together to the wild-type GG genotype (OR=4.77, p=0.04). A meta-analysis study showed that Transitional cell carcinoma could increase the risk of Transitional cell carcinoma slightly, but that result was not statically significant p=0.08.

Furthermore, an Association of TEP1/ rs2228041 Polymorphism with smoking status has been observed. There was no significant association between increasing Transitional cell carcinoma risks in never-smoker individuals caring for the polymorphic allele T of the TEP1/ rs2228041 polymorphism (p-value was 0.47. A statically significant increase in Transitional cell carcinoma risk was observed in smoker individuals caring for the wild-type C allele (OR=2.23, p=0.01). Moreover, highly association was discovered in smoker individuals carrying the T allele when comparing non-smoker individuals carrying the wild-type C allele with OR=7.02 and p=0.01. This significant association with increased Transitional cell carcinoma risk was also observed when comparing all ever-smoker individuals to non-smoker individuals of the current study (OR=2.51, p=0.03); the odds ratio was approximately similar to that of the ever-smoker with C allele genotype. That indicated that



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the C allele in smoker individual allele decreases the risk of Transitional cell carcinoma by OR of 0.28. Previous studies reported that smoking plus DNA repair gene SNPs could significantly increase Transitional cell carcinoma risk, supporting this finding [35, 36]. Tobacco smoking enhanced cellular proliferation and have a synergic effect on bladder carcinoma [37]. An example of that is by increasing the free radical substances such as nitric oxide [38]. Damaging these cells activate the proliferation mechanism to replace the cells. Furthermore, the TEP1/ rs2228041 SNP is a non-synonymous SNP that changing arginine to glutamine. Changing a strongly basic amino acid to a neutral amino acid (glutamine) could be very useful in changing protein structure and function, which could decrease protein activity [39] with the absence of telomerase activity. The telomere length will decrease rapidly and leading to DNA damaging. These data could explain developing Transitional cell carcinoma among smoker individuals carrying the polymorphic allele of the TEP1/ rs2228041. The correlation of the TEP1/ rs2228041 polymorphism and the stage of Transitional cell carcinoma was observed. For stage T2 High significant association in increasing Transitional cell carcinoma risk was observed in both (CT+TT) genotype and the polymorphic allele T of the TEP1/ rs2228041. Moreover, no association was observed in the Ta and T1. No previous study has described the association of TEP1/ rs2228041 SNP with the Transitional cell carcinoma stage. According to a recent study, the abnormal activity of this TEP caused by imbalanced genetic variation or gene expression may disrupt genome and chromosomal stability, promoting rapid cancer growth [33] . TEP1 Polymorphisms were found to enhance ovarian cancer progression through lowering the Mean Survival Time, and two-thirds of ovarian cancer patients with TEP1 Polymorphisms died due to progressive disease and chemotherapy resistance [40]. Different genes involved in telomere maintenance pathways were linked to chemotherapy resistance, which could be the reason of TCC's rapid progression to stage [40]. Furthermore, loss of telomere function and continued proliferation lead to broken chromosomes, breakage-fusion-bridge cycles, end-to-end fusions, and general genetic instability; the result is accelerated genetic changes accountable for more growth benefits as well as cancer cell development, which might indicate an increased risk of TCC for those who carry the polymorphic allele T of the TEP1/ rs2228041.In conclusion, TEP1/ rs2228041 showed an increased risk to have Transitional cell carcinoma among the Iraqi population. We also have the TEP1/ rs2228041 genotype along with the smoking highly increasing the risk to the development of the tumors. Moreover, the rate of the prognosis and developing Transitional cell carcinoma tumor is positively affected by the TEP1/ rs2228041 genotype, which makes it one of the future tools for monitoring the prognosis of Transitional cell carcinoma. We recommended a structural and functional analysis for the evaluation of the genetic, biological mechanism of this gene polymorphism.



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