Int J Clin Exp Pathol 2017;10(7):7776-7783
www.ijcep.com /ISSN:1936-2625/IJCEP0055787

*Original Article*

# Associations of *TERT* polymorphisms with hepatocellular carcinoma risk in a Han Chinese population

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Received April 19, 2017; Accepted April 26, 2017; Epub July 1, 2017; Published July 15, 2017

**Abstract:** Genetic association analysis and functional analysis have suggested that telomerase reverse transcriptase (*TERT*) gene affects the predisposition to various tumors. In this study, we wanted to explore the association between *TERT* variants and hepatocellular carcinoma (HCC) risk in a Han Chinese population via a case-control study of 473 HCC patients and 564 controls. Sequenom Mass-ARRAY platform was applied to determine the genotype of *TERT* polymorphisms in these subjects. Odds ratios and 95% confidence intervals that calculated by logistic regression analysis were used to assess the association under the genotype, dominant, recessive, and additive models. The "AA" genotype frequency of *TERT* rs2242652 in cases was significantly lower than in controls (1.69% versus 3.72%). We found two SNPs were associated with decreased risk of HCC with or without the adjustment for age and gender: rs10069690 under an additive model (adjusted OR = 0.77, 95% CI: 0.60-0.98, *P* = 0.038); rs2242652 under a dominant model (adjusted OR = 0.72, 95% CI: 0.54-0.95, *P* = 0.022) and an additive model (adjusted OR = 0.72, 95% CI: 0.56-0.92, *P* = 0.009). To our knowledge, the present study is the first to show the significant association between *TERT* polymorphisms and HCC susceptibility in a Han Chinese population from China, which may act as a potential prognostic biomarker in HCC patients.

**Keywords:** Hepatocellular carcinoma, *TERT*, single nucleotide polymorphisms (SNPs), association analysis

## Introduction

The incidence of HCC, the most common histological subtype of primary hepatic carcinoma, is increasing around the world in recent years, especially in China. HCC is affected by multifactor, including both environmental and genetic factors. Many candidate genes correlation analysis for this disease have been studied, such as *HLA-DP* gene polymorphisms have significant association with HCC in the Asian population [1]; *HMGB1* variants in the HCC susceptibility and progression in Chinese population [2]; *FasL* gene polymorphisms confer HCC risk in Egyptian individuals [3]; And SNPs in *TERT* and *CLPTM1L* and HCC predisposition in Chinese males [4].

Human telomerase is composed of telomerase reverse transcriptase (TERT), the catalytic subunit that synthesizes the repeat sequence TTAGGG of telomere, and telomerase RNA component (TERC), serves as the reverse transcription template [5]. Telomerase activation is restricted to the early stages of embryonic development and stem cells compartments in adult, however, it also occurs in some human cancers with a high level, such as in glioma, skin cancer, and lung carcinoma [4, 6]. Telomere locates at the end of chromosome which is critical for chromosome end protection and genomic stability. Telomere shortening occurs early in the initiation of epithelial carcinogenesis [7]. And telomere dysfunction promotes the chromosomal instability which plays an vital role in the initiation of carcinogenesis, while telomerase activation partially restores telomere length and genomic stability [8].

The TERT gene has been mapped to chromosome 5p15.33 and consisted of 16 exons and

**Table 1.** Primers used for the identification of *TERT* polymorphisms

| SNP | First PCRP (5'→3') | Second PCRP (5'→3') | UEP SEQ (5'→3') |
|---|---|---|---|
| rs10069690 | ACGTTGGATGCCTGTGGCTGCGGTGGCTG | ACGTTGGATGATGTGTGTTGCACACGGGAT | GGGATCCTCATGCCA |
| rs2242652 | ACGTTGGATGACAGCAGGACACGGATCCAG | ACGTTGGATGAGGCTCTGAGGACCACAAGA | gtcgGAGGACCACAAGAAGCAGC |
| rs2853677 | ACGTTGGATGATCCAGTCTGACAGTCGTTG | ACGTTGGATGGCAAGTGGAGAATCAGAGTG | gggtAATCAGAGTGCACCAG |
| rs2853676 | ACGTTGGATGTGTCTCCTGCTCTGAGACC | ACGTTGGATGCAAAACTAAGACCCAAGAGG | agatGGAAGTCTGACGAAGGC |

SNPs: single-nucleotide polymorphisms; PCRP: PCR primer; UEP: Un-extended mini-sequencing primer.

**Table 2.** Age and gender characteristics of HCC cases and controls

| Variable | Cases | Controls | *P* value |
|---|---|---|---|
| | (n = 473) | (n = 564) | |
| Gender | | | < 0.05 |
| Male | 390 (82.5%) | 339 (60.1%) | |
| Female | 83 (17.5%) | 225 (39.9%) | |
| Age, yr | 55.83 | 53.92 | < 0.05 |

15 introns spanning 35 kb of genomic DNA. It encodes the catalytic subunit of the telomerase reverse transcriptase, adds nucleotide repeats to chromosome ends. It is reported that this gene can influence the risk of various cancers, such as lung adenocarcinoma, upper tract urothelial carcinomas, glioma, and melanoma [9-12]. To date, many studies have suggested that the *TERT* promoter rs2853669 increases mortality and recurrence risks of HCC in Korean population [13]. There are prominent correlations with *TERT* polymorphisms and increased risk of HCC in a Han Chinese population from Northeast of China [4]. However, the associations between *TERT* variants and HCC risk in a Chinese Han population have not been investigated. And whether there are other SNPs in *TERT* that are correlated with HCC predisposition is still unknown in light of only one variant rs2736098 was reported [4]. Therefore, we performed a case-control study that was composed of 473 HCC patients and 564 controls from China was designed to research the potential association.

## Materials and methods

### *Subjects*

This gene association study was approved by the Ethics Committee of Haikou People's Hospital. The 473 HCC patients were newly diagnosed through clinical and histopathologic examinations in Haikou People's Hospital from March of 2013 to December of 2015. As controls we selected 564 non-cancer individuals from the Physical Examination Center of the same hospital. All subjects were unrelated Han Chinese population from China. Blood samples were collected from them with informed consent.

### *DNA isolation and SNPs genotyping*

Genomic DNA was extracted from peripheral blood leukocytes using the GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xi'an city, China). Then, we measured DNA concentration with the NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA) and quantified and diluted DNA with QIAgility to a final concentration of 20 ng/μl. We selected four *TERT* SNPs (rs10069690, rs2242652, rs2853677, rs2853676) that have been researched in different types of tumor, such as thyroid cancer, breast cancer, lung carcinoma, pancreatic cancer, and glioma [14-18], with minor allele frequencies more than 5% in Chinese Han Beijing population (International HapMapProject, version 28; http://www.hapmap.org) to preliminarily explore the potential correlation. Primers that were used for the identification of the four *TERT* SNPs were listed in **Table 1**. Sequenom MassARRAY RS1000 (Sequenom, SanDiego, CA) was applied to SNP genotyping. And data were analyzed and managed using Sequenom Typer 4.0 Software (Sequenom Co. Ltd) [19].

### *Statistical analysis*

We used SPSS 16.0 (SPSS, Chicago, IL, USA) and Microsoft Excel to conduct statistical analysis. Age and gender were compared between the cases and controls using Welch's *t* test and Pearson's $\chi^2$ test, respectively. Genotype frequencies of the four *TERT* SNPs were determined for deviation from Hardy-Weinberg Equilibrium (HWE) using Pearson's $\chi^2$ test. The associations of these polymorphisms genotypes with HCC risk were evaluated by odds ratios and 95% confidence intervals from multi-

**Table 3.** Allele distributions of *TERT* variants and their relationships with HCC susceptibility

| SNPs | Chromosome | Position | Allele | Minor allele frequency | | HWE *P* value | OR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | | | |
| rs10069690 | 5p15.33 | 1279790 | T/C | 0.135 | 0.171 | 0.6551 | 0.75 (0.59-0.96) | 0.021* |
| rs2242652 | 5p15.33 | 1280028 | A/G | 0.133 | 0.179 | 0.3914 | 0.70 (0.55-0.90) | 0.004* |
| rs2853677 | 5p15.33 | 1287194 | G/A | 0.370 | 0.369 | 0.7174 | 1.00 (0.84-1.20) | 0.966 |
| rs2853676 | 5p15.33 | 1288547 | T/C | 0.132 | 0.159 | 0.8744 | 0.81 (0.63-1.04) | 0.093 |

SNPs: single-nucleotide polymorphisms; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; 95% CI: 95% confidence interval. *P* values were calculated from Chi-square test/Fisher's exact test. *$P \leq 0.05$ indicates statistical significance.

**Table 4.** Genotype frequencies of rs10069690 and rs2242652 and their associations with HCC risk

| SNPs | Models | Genotype | Cases | Controls | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|---|---|
| | | | | | OR (95% CI) | *P* values | OR (95% CI) | *P* values |
| rs10069690 (C>T) | Genotype | CC | 353 | 386 | 1.00 | | 1.00 | |
| | | TC | 111 | 156 | 0.78 (0.59-1.03) | 0.082 | 0.80 (0.60-1.07) | 0.138 |
| | | TT | 8 | 18 | 0.49 (0.21-1.13) | 0.094 | 0.48 (0.20-1.15) | 0.098 |
| | Dominant | CC | 353 | 386 | 1.00 | | 1.00 | |
| | | TC+TT | 119 | 174 | 0.75 (0.57-0.98) | 0.038* | 0.77 (0.58-1.02) | 0.067 |
| | Recessive | CC+TC | 464 | 542 | 1.00 | | 1.00 | |
| | | TT | 8 | 18 | 0.52 (0.22-1.21) | 0.127 | 0.51 (0.21-1.21) | 0.126 |
| | Additive | - | - | - | 0.75 (0.59-0.96) | 0.022* | 0.77 (0.60-0.98) | 0.038* |
| rs2242652 (G>A) | Genotype | GG | 355 | 383 | 1.00 | | 1.00 | |
| | | AG | 110 | 160 | 0.74 (0.56-0.98) | 0.038* | 0.76 (0.57-1.02) | 0.066 |
| | | AA | 8 | 21 | 0.41 (0.18-0.94) | 0.035* | 0.41 (0.17-0.95) | 0.037* |
| | Dominant | GG | 355 | 383 | 1.00 | | 1.00 | |
| | | AA+AG | 118 | 181 | 0.70 (0.54-0.92) | 0.012* | 0.72 (0.54-0.95) | 0.022* |
| | Recessive | GG+AG | 465 | 543 | 1.00 | | 1.00 | |
| | | AA | 8 | 21 | 0.44 (0.20-1.01) | 0.054 | 0.44 (0.19-1.01) | 0.054 |
| | Additive | - | - | - | 0.71 (0.56-0.90) | 0.005* | 0.72 (0.56-0.92) | 0.009* |

SNPs: single-nucleotide polymorphisms; OR: odds ratio; 95% CI: 95% confidence interval. *P* values were calculated from unconditional logistic regression analysis. *$P \leq 0.05$ indicates statistical significance.

variate logistic regression analysis with or without adjustment for age and gender. And the relationships were also assessed under dominant, recessive, and additive genetic models using PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/). Finally, the SHEsis software platform (http://www.nhgg.org/analysis) and Haploview software package (version 4.2) were used to haplotype construction and analysis [20]. The correlations between *TERT* haplotypes and HCC risk were also calculated by logistic regression analysis. Statistical significance was set at a two-sided $P < 0.05$.

## Results

A total of 473 HCC cases and 564 controls from China were genotyped for *TERT* polymorphisms. We listed age and gender distributions in **Table 2** and found significant difference in them between cases and controls ($P < 0.05$). To eliminate the possible confounding effects caused by the difference, unconditional logistic regression analysis with adjustment for age and gender was applied to calculate Odds ratios.

**Table 3** shows the minor allele frequency distributions of *TERT* variants and their relationships with HCC susceptibility. The four SNPs were all in line with Hardy-Weinberg equilibrium in controls ($P > 0.05$). Significant differences were observed in allele frequencies of rs10069690T and rs2242652A between cases and controls (13.5% versus 17.1%; 13.3% versus 17.9%, respectively). And rs10069690T and rs2242652A were significantly correlated with decreased risk of HCC (OR = 0.75, 95% CI: 0.59-0.96, $P = 0.021$; OR = 0.70, 95% CI: 0.55-0.90, $P = 0.004$, respectively). In **Table 4** significant correlation with a reduced HCC susceptibility

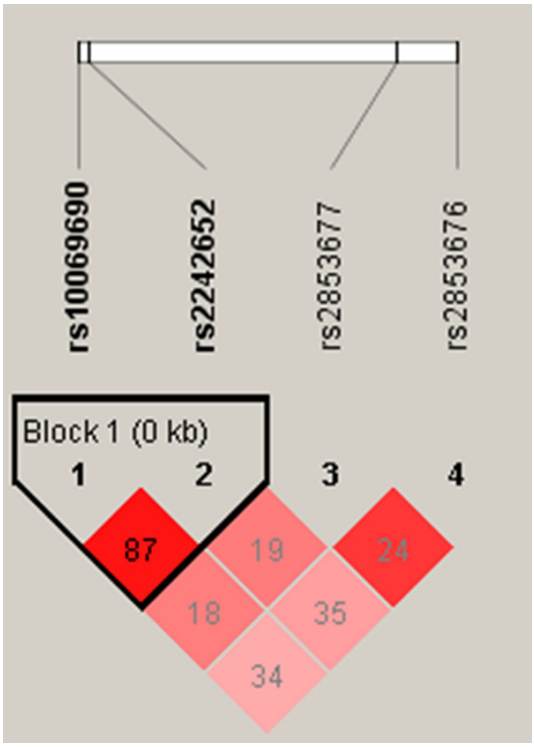


**Figure 1.** Haplotype block map for SNPs in the *TERT* gene.

was also found in "AA" genotype of rs2242652 when it compared with the wild "GG" genotype with or without adjustment by age and gender (adjusted OR = 0.41, 95% CI: 0.17-0.95, *P* = 0.037).

After evaluating the potential association under dominant, recessive, and additive genetic models, we found two SNPs were associated with decreased risk of HCC with or without the adjustment: rs10069690 under an additive model (adjusted OR = 0.77, 95% CI: 0.60-0.98, *P* = 0.038); rs2242652 under a dominant model (adjusted OR = 0.72, 95% CI: 0.54-0.95, *P* = 0.022) and an additive model (adjusted OR = 0.72, 95% CI: 0.56-0.92, *P* = 0.009) (**Table 4**).

In addition, the candidate SNPs (rs10069690-rs2242652) in *TERT* exhibited strong linkage. In **Figure 1**, the red squares of the *TERT* linkage disequilibrium block showed statistically significant linkage between the two polymorphisms. We listed the haplotypes with frequencies of more than 0.05 and their associations with HCC risk in **Table 5**. Haplotype "TA" was associated with a reduced risk of HCC (adjusted OR = 0.77, 95% CI: 0.60-0.99, *P* = 0.040), on the contrary, "CG" was correlated with an increased risk of HCC (adjusted OR = 1.37, 95% CI: 1.07-1.75, *P* = 0.013).

## Discussion

In the present study, we genotyped four *TERT* polymorphisms (rs10069690, rs2242652, rs2853677, rs2853676) in HCC patients and healthy controls, and our results showed a statistically significant association between *TERT* variants and HCC susceptibility: the "T" allele of rs10069690 and the "A" allele of rs2242652 were associated with decreased risk of HCC in a Han Chinese population. These findings suggest that some *TERT* polymorphisms identified in other types of tumor are also correlated with HCC risk.

Telomerase reverse transcriptase, encoded by the *TERT* gene, is an essential component of telomerase. Telomerase expression is restricted to stem cell and embryonic tissue, but in some human cancers, telomerase activity is higher than in normal tissues in adult. The high expression of telomerase confers a indefinitely replicative potentiality via the restoration of telomere length which may be involved in carcinogenesis [21]. On the other hand, as we know, the p53 is an important molecule involved in regulating cellular response to DNA damage, such as induced by telomere dysfunction and shortening, and repairing or eliminating cells [22]. In the setting of deactivated p53, telomere dysfunction and shortening can result in the chromosomal instability which may promote carcinogenesisin epithelial compartments [5]. Therefore, it is difficult to determine long or short telomere length is correlated with tumor susceptibility.

Studies have demonstrated that *TERT* rs10069690 could confer an increased risk of thyroid cancer, breast cancer, and ovarian cancer etc or a reduced predisposition to multiple myeloma [14, 15, 23, 24]. As for *TERT* rs2242652, it was either associated with increased risk of breast cancer or decreased susceptibility to multiple myeloma [24, 25]. These differences may be due to the dysregulated *TERT* expression in most kinds of tumors. A recent study by Bojesen et al. suggested rs10069690 and rs2242652 respectively contain a silencer of the *TERT* promoter and form a truncated *TERT*

**Table 5.** *TERT* haplotype frequencies and their correlations with the risk of HCC

| Haplotype block | Haplotype frequencies | | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|
| | Case | Control | OR (95% CI) | *P* | OR (95% CI) | *P* |
| TA | 0.13 | 0.17 | 0.75 (0.59-0.96) | 0.018* | 0.77 (0.60-0.99) | 0.040* |
| CG | 0.86 | 0.82 | 1.38 (1.08-1.75) | 0.009* | 1.37 (1.07-1.75) | 0.013* |

OR: odds ratio; 95% CI: 95% confidence interval. *P* values were calculated from unconditional logistic regression analysis. *$P \leq 0.05$ indicates statistical significance.

splice variant which further reduce gene expression[26].Kote-Jaraietal.observedthatrs22-42652 was related to a decreased *TERT* expression in prostate cancer [27]. In the present study, we found *TERT* rs10069690 and rs2242652 served as protective factors for the formation of HCC, which may be due to the reduced expression of TERT protein by these SNPs and synthesis of telomerase with shorter telomere length.

However, this study also had several limitations. First, although age and gender were taken into consideration for the unconditional logistic regression, other risk factors, for instance, infection of hepatitis B virus, drinking and smoking status, and diet were not analyzed in this study. Second, we have not genotyped all the *TERT* variants which may lead to omission of some significant SNPs. Third, our study is limited by relatively small sample size, and lack of randomization to conditions.

To our knowledge, this study is the first to present the significant correlation between *TERT* polymorphisms and HCC susceptibility in a Han Chinese population from China, which may provide theoretical foundation for others to further study the potential association and new information for screening of HCC predisposed population in clinical practice.

## Acknowledgements

This research was supported by (a) National Natural Science Foundation of China grants (81460450); (b) Natural Science Foundation of Hainan Province grants (309115 and 817379 and 20168312); (c) Hainan Province Natural Science Foundation of Innovation Research Team Project (2017CXTD010).

## Disclosure of conflict of interest

None.

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