Single nucleotide polymorphisms in telomere length-related genes are associated with hepatocellular carcinoma risk in the Chinese Han population

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Abstract

Background: Single nucleotide polymorphisms [SNPs] in telomere-related genes are associated with a high risk of hepatocellular carcinoma (HCC). In this study, we investigated the SNPs of telomere length-related genes and their correlation with HCC risk in the Chinese Han population.

Materials and methods: A total of 473 HCC patients and 564 healthy volunteers were recruited. Overall, 42 SNPs distributed in telomere-related genes were selected and identified. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: We found rs6713088 (OR = 1.27, 95% CI = 1.07–1.52, p = 0.007), rs843711 (OR = 1.29, 95% CI = 1.09–1.54, p = 0.004) and rs843706 (OR = 1.30, 95% CI = 1.09–1.55, p = 0.003) in the ACYP2 gene, rs10936599 (OR = 1.21, 95% CI = 1.02–1.44, p = 0.032) in the TERC gene and rs7708392 (OR = 1.24, 95% CI = 1.00–1.52, p = 0.042) in the TNIP1 gene were associated with high HCC risk (OR > 1). In contrast, rs1682111 (OR = 0.77, 95% CI = 0.64–0.94, p = 0.008) in the ACYP2 gene, rs2320615 (OR = 0.79, 95% CI = 0.64–0.99, p = 0.038) in the NAF1 gene, rs10069690 (OR = 0.75, 95% CI = 0.59–0.96, p = 0.021) and rs2242652 (OR = 0.70, 95% CI = 0.55–0.90, p = 0.004) in the TERT gene were associated with low HCC risk (OR < 1). Based on genotype frequency distributions, rs6713088, rs843645, rs843711 and rs843706 located in the ACYP2 gene as well as rs10936599 in the TERC gene were associated with a high incidence of HCC (p < 0.05). In addition, these SNPs in these genes could form a linkage imbalance haplotype. Specifically, the haplotype 'GC' formed by rs10069690 and rs2242652 within the ACYP2 gene as well as rs10936599 in the TERT gene were associated with a high risk of HCC (p < 0.05).

Conclusion: SNPs in ACYP2, TERC, TERT and other genes were correlated with HCC risk in the Chinese Han population. These data may provide new insights into early diagnosis and screening of HCC.

Keywords: case–control study, gene variation, hepatocellular carcinoma, SNP, telomere length-related genes

Introduction

Hepatocellular carcinoma (HCC) is one of the most common deadly cancer types in China. Chinese HCC cases represent greater than 50% of new liver cancer cases in the world every year.1,2 Viral hepatitis, excessive alcohol consumption, aflatoxin and metabolic diseases are causative agents of HCC.3–6 In addition, genomic alterations including abnormal telomere length are also important risk factors for the occurrence and development of HCC.7,8 However, the precise pathogenic mechanism of HCC remains unclear.

Telomeres are a short special structure located at the end of chromosomes that maintain the integrity of chromosome and regulate the cell cycle.9

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In normal cells, dysfunctional telomeres trigger damage to DNA structure or function and are also associated with cellular senescence processes. Chromosomes shorten with each cell division. However, some highly proliferating cells, such as germ cells and cancer cells, prevent chromosome shortening by expressing telomerase. Many studies show that abnormal telomere length is associated with an increased risk of cancers including HCC.

The ACYP2 (acylphosphatase 2) gene coding for acylphosphatase, which hydrolyzes multiple membrane proteins, regulates the glycolysis pathway, pyruvate metabolism and cell apoptosis and also affects telomere length. Previous studies have reported that ACYP2 polymorphisms are associated with the shorter telomere length in the European population. The TERC gene (telomerase RNA component) is widely distributed in embryonic tissues, including undifferentiated neural epithelial tissues and interstitial tissues; is used as a template for telomere DNA synthesis; maintains telomere stability; and affects telomere length.

The NAFI (nuclear assembly factor 1) gene plays a vital role in maintaining telomerase activity and function by impacting the telomerase complex. TERT (telomerase reverse transcriptase) is involved in maintaining telomere length and is highly expressed in tumor tissues. Myc is an important transcriptional regulator of TERT that directly controls its expression by promoter binding. The TNIP1 (TNFAIP3 interacting protein 1) gene plays an important role in the immune system and homeostasis by regulating nuclear transcription factor κB activation and is related to telomere length. The OBFC1 (oligonucleotide/oligosaccharide-binding fold-containing protein 1) gene protects the telomere structure from degradation, maintains telomere length and participates in DNA metabolism. The MPHOSPH6 (m-phase phosphoprotein 6) gene, which encodes for a RNA-binding protein, participates in the synthesis of 5.8s ribosomal rRNA from a 7S ribosomal precursor, plays a role in the recruitment of ribosomal precursor and is also related to telomere length. The ZNF208 (zinc finger protein 208) gene, which is located on chromosome 19 (19p12), regulates gene transcription by binding downstream genes and maintains telomere length.

Mutations in telomere-related genes can lead to excessive gain or loss of function and may cause many diseases, including cancers. However, the relationship between SNPs in telomere-related genes and the incidence of HCC remains poorly understood. Therefore, we conducted a case–control study to investigate the association between SNPs in telomere length-related genes and HCC risk. These data may provide new insights and a theoretical basis for the pathogenesis, early diagnosis and treatment of HCC.

Materials and methods

Study participants

We applied a case–control study to investigate the association of telomere-related genes with the occurrence and development of HCC. In total, 473 participants with newly diagnosed HCC and 564 normal individuals with a healthy physical examination at the First Affiliated Hospital and Second Affiliated Hospital of Xi’an Jiaotong University between June 2015 and October 2017 were recruited. Blood samples were collected from all participants. Particularly, all patients with HCC were identified based on pathology, cytology, imaging examinations (magnetic resonance imaging and/or computerized tomography), and serum alpha-fetoprotein level according to the standard of diagnosis and treatment of primary liver cancer published by the Ministry of Public Health of China. None of the patients with HCC previously received either chemotherapy or radiotherapy or had any other cancers. Individuals were excluded from the study if they had hepatitis C virus, human immunodeficiency virus antibodies, autoimmune disease, active schistosomiasis, or received prior treatments such as local ablation therapy and transarterial chemoembolization. Meanwhile, 564 healthy volunteers in good mental condition were included as a control group. None of the healthy volunteers had a previous history of hepatic disease such as viral hepatitis, cirrhosis and tumor history. All of them had liver functions within the reference ranges, normal liver and biliary system ultrasound, normal clinical and laboratory examination results and negative serological findings for autoimmune and viral hepatic diseases. All patients with HCC and healthy volunteers were born and lived in the same area (Shaanxi, China). This study was approved by the Human Research Committee of the First Affiliated Hospital and the Second Affiliated Hospital of Xi’an Jiaotong University.
The approval ID was 2015-172. Written informed consent was obtained, and informed consent for blood analysis was obtained from all participants prior to the study.

**Questionnaire survey and sample collection**

Face-to-face interviews were performed using an epidemiological questionnaire survey to gather information on the participants. The questionnaire included content on participants’ basic information (age and sex). Detailed information is provided in Table 1. Moreover, 5 ml of peripheral blood was collected from each participant using vacuum EDTA anticoagulant tubes. Blood samples were stored at –80°C.

**SNP selection**

After screening, 42 SNPs distributed in nine telomere length-related genes with minor allele frequencies >5% in the HapMap Chinese Han Beijing population were selected from the 1000 Genomes Project database (www.1000genomes.org), the National Center for Biotechnology Information dbSNP database (www.ncbi.nlm.nih.gov/projects/SNP) and previously published telomere length polymorphisms reported in sequencing experiments. The 42 SNPs were located in ACYP2, TERC, TERT, NAF1, TNIP1, OBFC1, MPHOSPH6, ZNF208 and RTEL1 genes. The correlation between the above SNPs and HCC susceptibility were analyzed. The specific primer SNPs were listed in Supplemental Table 1.

**Genotyping**

Whole genomic DNA was extracted from blood samples using a GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd., Xi’an, China). DNA concentration and purity were determined using NanoDrop 2000 (Gene Company Ltd., Hong Kong, China). Sample concentrations <10 ng/ul were excluded. The purity of the DNA sample was determined based on the OD260/OD280 ratio. In our experiment, the acceptable range of the sample ratio was 1.7–2.0. We used Agena MassARRAY Assay Design 3.0 Software to design a Multiplexed SNP MassEXTEND assay. Sequenom MassARRAY RS1000 was applied for genotyping, and data were analyzed using Sequenom Typer 4.0 software.

**Statistical analysis**

Data analysis was performed using Microsoft Excel (Redmond, WA, USA) and SPSS 22.0 statistical package (SPSS, Chicago, IL, USA). The \( p \) values reported in this study were two sided, and \( p < 0.05 \) was considered statistically significant. The frequency of all SNPs in the control group was assessed for Hardy–Weinberg equilibrium (HWE) using Fisher’s exact tests. The age and sex distribution differences between the two groups were calculated using Chi-square tests. Categorical variable differences in characteristics between all allele frequencies of SNPs in case and control groups were also analyzed using the Chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) of genotypes were determined using unconditional logistic regression with adjustment for age and sex. Different models (genotype, dominant, recessive, and additive model) were performed using PLINK software (www.cog-genomics.org/plink2), to characterize the potential association of each gene polymorphism with HCC risk. We also applied Haploview software (version 4.2) to perform haplotype analysis in 564 control samples. We used

| Characteristics     | HCC \((n = 473)\) | Percentage (\%) | Normal \((n = 564)\) | Percentage (\%) | \( p \) value |
|---------------------|------------------|----------------|----------------------|----------------|------------|
| Age (years)         |                  |                |                      |                |            |
| ⩾50                 | 330              | 69.8           | 406                  | 72.0           | 0.010*     |
| <50                 | 143              | 30.2           | 158                  | 28.0           |            |
| Sex                 |                  |                |                      |                | <0.0001*   |
| Male                | 390              | 82.5           | 339                  | 60.1           |            |
| Female              | 83               | 17.5           | 225                  | 39.9           |            |

*\( p < 0.05. \) HCC, hepatocellular carcinoma.

Table 1. General characteristics in patients with HCC and healthy volunteers (‘normal’).
the parameter $r^2 (r^2 \leq 1)$ to measure the degree of linkage disequilibrium analysis between the two SNP loci. Haplotypes were divided into haplotype blocks using the parameter $D'$ confidence interval, $|D'| \leq 1$.

Results

General demographic characteristics of patients
The experiments were performed using the case–control method. This study included a total of 473 patients with HCC and 564 healthy volunteers. In the HCC group, the average age was 55.83 ± 12.20 years. There were 330 people older than 50 years, and 143 people younger than 50 years in this group. The age in the healthy group was 53.92 ± 11.50 years. There were 406 people older than 50 years, and 158 people who were younger than 50 years in this group. A significant difference in age was noted between these two groups ($p = 0.01$). In the HCC group, 390 were male, accounting for 82.5% of cases, and 83 were female, accounting for 17.5% of cases. The control group included 339 males, accounting for 60.1% of cases, and 225 females, accounting for 39.9%. A significant difference in sex distribution was noted between the two groups ($p < 0.0001$). Given that the family history of tumors in the control group was limited (only eight cases with a family history of tumors in normal healthy group, while 98 cases had a family history of tumors in the HCC group), we did not include the factor of family history of tumors in the logistic regression models to avoid model bias. Detailed characteristics of the participants and the analysis of results are shown in Table 1 and Figure 1.

Relationships between SNPs and HCC
Among all gene loci, the HWE value of rs11859599 (MPHOSPH6) is lower than 0.05 (HWE = 0.0281), which is not consistent with the Hardy–Weinberg law of equilibrium. Thus, this gene SNP was excluded. Among the detected SNP loci, based on the alleles distribution, we found that rs6713088 (OR = 1.27, 95% CI = 1.07–1.52, $p = 0.007$), rs843711 (OR = 1.29, 95% CI = 1.09–1.54, $p = 0.004$), and rs10936599 (OR = 1.21, 95% CI = 1.02–1.44, $p = 0.032$) of the ACYP2 gene; rs10936599 (OR = 1.21, 95% CI = 1.02–1.44, $p = 0.032$) of the TERC gene; and rs7708392 (OR = 1.24, 95% CI = 1.00–1.52, $p = 0.042$) of the TNIP1 gene were associated with an increased risk of HCC (OR > 1) [Figure 2(a)]. Rs1682111 (OR = 0.77, 95% CI = 0.64–0.94, $p = 0.008$) of the ACYP2 gene, rs2320615 (OR = 0.79, 95% CI = 0.64–0.99, $p = 0.038$) of the NAF1 gene, and rs10069690 (OR = 0.75, 95% CI = 0.59–0.96, $p = 0.021$) and rs2242652 (OR = 0.70, 95% CI = 0.55–0.90, $p = 0.004$) of the TERT gene were associated with a reduced risk of HCC (OR < 1) [Figure 2(b)]. Specific data are presented in Table 2.

Relationships between different genotypes and HCC
Next, the relationships between different genotypes and HCC were analyzed. We found that the rs6713088 genotype in the ACYP2 gene was

![Figure 1. Detailed characteristics and analysis of the participants are shown. The age and sex distribution of the participants are presented. *p < 0.05.](image-url)
significantly associated with the high risk of HCC in both the additive model (OR = 1.23, 95% CI: 1.02–1.48, \( p = 0.028 \)) and dominant model (OR = 1.32, 95% CI: 1.01–1.74, \( p = 0.043 \)). Furthermore, other loci remarkably associated with high risk of HCC included rs843645 (codominant model: OR = 1.40, 95% CI = 1.07–1.82 for G/T, OR = 0.96, 95% CI = 0.57–1.60 for G/G, \( p = 0.038 \); dominant model: OR = 1.32, 95% CI = 1.02–1.70, \( p = 0.033 \)), rs843711 (additive model: OR = 1.26, 95% CI: 1.06–1.51, \( p = 0.010 \); codominant model: OR = 1.13, 95% CI: 0.84–1.52 for T/C, OR = 1.62, 95% CI: 1.13–2.31 for T/T, \( p = 0.023 \); recessive model: OR = 1.50, 95% CI: 1.11–2.03, \( p = 0.009 \)), and rs843706 (additive model: OR = 1.26, 95% CI: 1.06–1.51, \( p = 0.010 \); codominant model: OR = 1.14, 95% CI: 0.84–1.53 for A/C, OR = 1.62, 95% CI: 1.13–2.31 for A/A, \( p = 0.024 \); recessive model: OR = 1.49, 95% CI: 1.10–2.02, \( p = 0.009 \)) in the \( ACYP2 \) gene as well as rs10936599 (additive model: OR = 1.20, 95% CI: 1.01–1.43, \( p = 0.038 \)) in the \( TERC \) gene.

Meanwhile, we also identified three loci significantly associated with a low risk of HCC, including rs1682111 in the \( ACYP2 \) gene as well as rs10936599 (additive model: OR = 1.20, 95% CI: 1.01–1.43, \( p = 0.038 \)) in the \( TERC \) gene. Moreover, we also identified three loci significantly associated with a low risk of HCC, including rs1682111 in the \( ACYP2 \) gene as well as rs10936599 (additive model: OR = 1.20, 95% CI: 1.01–1.43, \( p = 0.038 \)) in the \( TERC \) gene.

**Figure 2.** Analysis of the relationships between SNPs and HCC. (a) SNPs associated with high risk of HCC are presented. (b) SNPs associated with low risk of HCC are presented.

HCC, hepatocellular carcinoma; SNP, single nucleotide polymorphism.

### Relationships between haplotypes and HCC

D’ and \( r^2 \) were used to measure the degree of linkage disequilibrium between the two SNPs. D’ CIs were used to classify the haplotypes. Overall, eight main linkage blocks were observed across the loci [Figure 3(a–h)]. In the \( ACYP2 \) gene on chromosome 2, rs168211, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711 and rs11896604 constituted block 1 that was 51 kb in length. Rs843706 and rs17015754 in the \( ACYP2 \) gene also constituted block 2 that was 16 kb in length [Figure 3(a)]. In the \( TERC \) gene on chromosome 3, rs35073794 and rs10939599 constituted a block [Figure 3(b)]. In the \( TERT \) gene on chromosome 5, rs10069690 and rs2242652 constituted block 1 [Figure 3(c)]. In the \( TNIP1 \) gene, rs7708392 and rs10036748 also constituted block 1 that was 0 kb in length [Figure 3(d)]. In the \( OBFC1 \) gene on chromosome 10, rs9325507, rs3814220, rs12765878 and rs11191865 constituted block 1 that was 27 kb in length [Figure 3(e)]. In the \( MPHOSPH6 \) gene on chromosome 16, rs1056675, rs1056654, rs3751862 and rs2967361 constituted block 1 that was 21 kb in length [Figure 3(f)]. In the \( ZNF208 \) gene on chromosome 19, rs2188972, rs2188971, rs8103163 and rs7248488 constituted block 1 that was 39 kb
Table 2. Frequency distributions of alleles and the information of SNPs in HCC and healthy volunteers (‘normal’).

| SNP      | Gene | Chromosome | Function     | Allele (A/B) | Allele frequency HWE | p value | OR (95% CI) | p       |
|----------|------|------------|--------------|--------------|----------------------|---------|-------------|---------|
| rs6713088| ACYP2| 2          | Intron       | G            | 0.452 0.393          | 0.379 1.27 (1.07–1.52) | 0.007*  |
|          |      |            |              | C            | 0.548 0.607          |         |             |         |
| rs12621038| ACYP2| 2          | Intron       | T            | 0.445 0.440          | 0.608 1.02 (0.86–1.22) | 0.813   |
|          |      |            |              | C            | 0.555 0.560          |         |             |         |
| rs1682111| ACYP2| 2          | Intron       | A            | 0.275 0.329          | 0.775 0.77 (0.64–0.94) | 0.008*  |
|          |      |            |              | T            | 0.725 0.671          |         |             |         |
| rs843752 | ACYP2| 2          | Intron       | G            | 0.296 0.266          | 0.518 1.16 (0.95–1.40) | 0.141   |
|          |      |            |              | T            | 0.704 0.734          |         |             |         |
| rs10439478| ACYP2| 2          | Intron       | C            | 0.427 0.402          | 0.382 1.11 (0.93–1.32) | 0.258   |
|          |      |            |              | A            | 0.573 0.598          |         |             |         |
| rs17045754| ACYP2| 2          | Intron       | C            | 0.197 0.167          | 0.761 1.22 (0.98–1.53) | 0.077   |
|          |      |            |              | G            | 0.803 0.833          |         |             |         |
| rs843720 | ACYP2| 2          | Intron       | G            | 0.303 0.342          | 0.779 0.84 (0.69–1.01) | 0.057   |
|          |      |            |              | T            | 0.697 0.658          |         |             |         |
| rs843645 | ACYP2| 2          | Downstream   | G            | 0.282 0.252          | 0.263 1.17 (0.96–1.42) | 0.116   |
|          |      |            |              | T            | 0.718 0.748          |         |             |         |
| rs11125529| ACYP2| 2         | Downstream   | A            | 0.185 0.164          | 0.644 1.16 (0.92–1.46) | 0.201   |
|          |      |            |              | C            | 0.815 0.836          |         |             |         |
| rs12615793| ACYP2| 2         | Downstream   | A            | 0.201 0.178          | 0.315 1.16 (0.93–1.45) | 0.181   |
|          |      |            |              | G            | 0.799 0.822          |         |             |         |
| rs843711 | ACYP2| 2          | Downstream   | T            | 0.501 0.437          | 1.000 1.29 (1.09–1.54) | 0.004*  |
|          |      |            |              | C            | 0.499 0.563          |         |             |         |
| rs11896604| ACYP2| 2         | Downstream   | G            | 0.214 0.185          | 0.675 1.20 (0.97–1.49) | 0.098   |
|          |      |            |              | C            | 0.786 0.815          |         |             |         |
| rs843706 | ACYP2| 2          | 3’ UTR       | A            | 0.504 0.439          | 1.000 1.30 (1.09–1.55) | 0.003*  |
|          |      |            |              | C            | 0.496 0.561          |         |             |         |
| rs35073794| TERC | 3          | Downstream   | A            | 0.010 0.006          | 1.000 1.54 (0.57–4.15) | 0.389   |
|          |      |            |              | G            | 0.090 0.994          |         |             |         |
| rs10936599| TERC | 3          | Promoter     | C            | 0.484 0.437          | 0.123 1.21 (1.02–1.44) | 0.032*  |
|          |      |            |              | T            | 0.516 0.563          |         |             |         |

(Continued)
| SNP         | Gene   | Chromosome | Function | Allele [A/B] | Allele frequency | HWE p value | OR (95% CI) | p      |
|-------------|--------|------------|----------|--------------|------------------|-------------|-------------|--------|
| rs2320615   | NAF1   | 4          | Intron   | A            | 0.180            | 1.000       | 0.79 [0.64–0.99] | 0.038*  |
|             |        |            |          | G            | 0.820            | 0.784       |             |        |
| rs10069690  | TERT   | 5          | Intron   | T            | 0.135            | 0.655       | 0.75 [0.59–0.96] | 0.021*  |
|             |        |            |          | C            | 0.865            | 0.829       |             |        |
| rs2242652   | TERT   | 5          | Intron   | A            | 0.133            | 0.391       | 0.70 [0.55–0.90] | 0.004*  |
|             |        |            |          | G            | 0.867            | 0.821       |             |        |
| rs2853677   | TERT   | 5          | Intron   | G            | 0.370            | 0.717       | 1.00 [0.84–1.20] | 0.966   |
|             |        |            |          | A            | 0.630            | 0.631       |             |        |
| rs2853676   | TERT   | 5          | Intron   | T            | 0.132            | 0.874       | 0.81 [0.63–1.04] | 0.092   |
|             |        |            |          | C            | 0.868            | 0.841       |             |        |
| rs3792792   | TNIP1  | 5          | Intron   | C            | 0.063            | 1.000       | 1.25 [0.86–1.81] | 0.240   |
|             |        |            |          | T            | 0.937            | 0.949       |             |        |
| rs7708392   | TNIP1  | 5          | Intron   | G            | 0.247            | 0.444       | 1.24 [1.00–1.52] | 0.042*  |
|             |        |            |          | C            | 0.753            | 0.791       |             |        |
| rs10036748  | TNIP1  | 5          | Intron   | C            | 0.247            | 0.527       | 1.23 [1.00–1.51] | 0.053   |
|             |        |            |          | T            | 0.753            | 0.789       |             |        |
| rs9325507   | OBFC1  | 10         | Intron   | T            | 0.316            | 0.073       | 0.91 [0.75–1.09] | 0.306   |
|             |        |            |          | C            | 0.684            | 0.663       |             |        |
| rs3814220   | OBFC1  | 10         | Intron   | G            | 0.317            | 0.090       | 0.91 [0.76–1.09] | 0.317   |
|             |        |            |          | A            | 0.683            | 0.662       |             |        |
| rs12765878  | OBFC1  | 10         | Intron   | C            | 0.314            | 0.090       | 0.90 [0.75–1.08] | 0.250   |
|             |        |            |          | T            | 0.686            | 0.662       |             |        |
| rs11191865  | OBFC1  | 10         | Intron   | A            | 0.315            | 0.090       | 0.90 [0.75–1.08] | 0.271   |
|             |        |            |          | G            | 0.685            | 0.662       |             |        |
| rs9420907   | OBFC1  | 10         | Intron   | C            | 0.011            | 1.000       | 1.08 [0.46–2.56] | 0.859   |
|             |        |            |          | A            | 0.989            | 0.990       |             |        |
| rs1056675   | MPHOSPH6| 16         | 3' UTR   | C            | 0.421            | 0.725       | 1.11 [0.93–1.32] | 0.260   |
|             |        |            |          | T            | 0.579            | 0.603       |             |        |
| rs1056654   | MPHOSPH6| 16         | 3' UTR   | A            | 0.317            | 0.851       | 0.90 [0.75–1.08] | 0.249   |
|             |        |            |          | G            | 0.683            | 0.659       |             |        |
Table 2. (Continued)

| SNP          | Gene      | Chromosome | Function | Allele (A/B) | Allele frequency | HWE p value | OR (95% CI) | p     |
|--------------|-----------|------------|----------|--------------|------------------|-------------|-------------|-------|
| rs3751862    | MPHOSPH6  | 16         | 3' UTR   | C            | 0.059            | 1.000       | 1.03 (0.71–1.48) | 0.887 |
|              |           |            |          | A            | 0.941            | 0.942       |             |       |
| rs11859599   | MPHOSPH6  | 16         | Intron   | C            | 0.201            | 0.028*      | 0.97 (0.78–1.20) | 0.766 |
|              |           |            |          | G            | 0.799            | 0.793       |             |       |
| rs2967361    | MPHOSPH6  | 16         | Intron   | T            | 0.234            | 0.068       | 1.05 (0.86–1.30) | 0.611 |
|              |           |            |          | G            | 0.766            | 0.776       |             |       |
| rs2188972    | ZNF208    | 19         | 3' UTR   | A            | 0.511            | 0.501       | 1.08 (0.91–1.28) | 0.378 |
|              |           |            |          | G            | 0.489            | 0.509       |             |       |
| rs2188971    | ZNF208    | 19         | 3' UTR   | T            | 0.304            | 0.473       | 1.07 (0.89–1.30) | 0.472 |
|              |           |            |          | C            | 0.696            | 0.710       |             |       |
| rs8103163    | ZNF208    | 19         | Intron   | A            | 0.305            | 0.474       | 1.07 (0.89–1.30) | 0.464 |
|              |           |            |          | C            | 0.695            | 0.710       |             |       |
| rs7248488    | ZNF208    | 19         | Intron   | A            | 0.304            | 0.414       | 1.07 (0.88–1.29) | 0.498 |
|              |           |            |          | C            | 0.696            | 0.709       |             |       |
| rs8105767    | ZNF208    | 19         | Intron   | G            | 0.304            | 0.481       | 1.03 (0.85–1.24) | 0.774 |
|              |           |            |          | A            | 0.696            | 0.702       |             |       |
| rs6089953    | RTEL1     | 20         | Intron   | G            | 0.292            | 0.473       | 1.02 (0.84–1.23) | 0.841 |
|              |           |            |          | A            | 0.708            | 0.712       |             |       |
| rs6010621    | RTEL1     | 20         | Intron   | G            | 0.263            | 0.833       | 0.95 (0.78–1.15) | 0.600 |
|              |           |            |          | T            | 0.737            | 0.726       |             |       |
| rs4809324    | RTEL1     | 20         | Intron   | C            | 0.133            | 0.838       | 1.16 (0.89–1.51) | 0.261 |
|              |           |            |          | T            | 0.867            | 0.884       |             |       |
| rs2297441    | RTEL1     | 20         | Intron   | A            | 0.326            | 0.700       | 1.02 (0.85–1.22) | 0.855 |
|              |           |            |          | G            | 0.674            | 0.678       |             |       |

CI, confidence interval; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single nucleotide polymorphism. *p < 0.05.

in length [Figure 3(g)]. In the RTEL1 gene on chromosome 20, rs6089953, rs6010621 and rs4809324 constituted block 1 that was 27 kb in length [Figure 3(h)]. To further analyze the correlation between the haplotypes formed by these detected SNP loci in this experiment and the risk of HCC, we processed the data by both unadjusted analysis and unconditional logistic regression analysis after adjusting for age and sex. The data obtained were analyzed using HAPSTAT software. The results were summarized in Table 4. Taken together, haplotype analysis revealed that haplotype ‘CG’ in the TERT gene (OR = 1.37, 95% CI: 1.07–1.75, p = 0.013) increased the risk of HCC. Furthermore, the haplotype ‘ATATCGCC’ in the ACYP2 gene (OR = 0.76, 95% CI:
Table 3. Distribution of different SNP genotypes and risk analysis of HCC.

| Gene | SNP      | Model     | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|------|----------|-----------|----------|-----------|---------------|----------------|---------------------|
|      |          |           |          | n (%)     | n (%)         | OR (95% CI)    | p                   | OR (95% CI)         | p         |
| ACYP2| rs6713088| Codominant| C/C      | 138 (29.2%)| 202 (35.9%)  | 1              | 1                   | 1                   |           |
|      |          |           | G/C      | 242 (51.2%)| 279 (49.6%)  | 1.27 (0.96–1.67)| 0.023*             | 1.27 (0.95–1.69)   | 0.087     |
|      |          |           | G/G      | 93 (19.7%) | 82 (14.6%)   | 1.66 (1.15–2.40)| 0.015*             | 1.49 (1.02–2.18)  |           |
|      |          | Dominant  | C/C      | 138 (29.2%)| 202 (35.9%)  | 1              | 1                   | 1                   |           |
|      |          |           | G/C+G/G  | 335 (70.9%)| 361 (64.2%)  | 1.36 (1.05–1.77)| 0.022*             | 1.32 (1.01–1.74)  | 0.043*    |
|      |          | Recessive | C/C+G/C  | 380 (80.4%)| 481 (85.5%)  | 1              | 1                   | 1                   |           |
|      |          |           | G/G      | 93 (19.7%) | 82 (14.6%)   | 1.44 (1.04–1.99)| 0.030*             | 1.29 (0.92–1.81)  | 0.138     |
|      |          | Log-additive| –        | –       | –            | 1.29 (1.08–1.54)| 0.006*             | 1.23 (1.02–1.48)  | 0.028*    |
| ACYP2| rs12621038| Codominant| C/C      | 139 (29.5%)| 180 (31.9%)  | 1              | 1                   | 1                   |           |
|      |          |           | T/C      | 245 (52.0%)| 271 (48.1%)  | 1.17 (0.88–1.55)| 0.462             | 1.28 (0.96–1.71)  | 0.228     |
|      |          |           | T/T      | 87 (18.5%) | 112 (19.9%)  | 1.01 (0.70–1.44)| 0.561             | 1.08 (0.75–1.56)  |           |
|      |          | Dominant  | C/C      | 139 (29.5%)| 180 (31.9%)  | 1              | 1                   | 1                   |           |
|      |          |           | T/C+T/T  | 332 (70.5%)| 383 (68.0%)  | 1.12 (0.86–1.46)| 0.394             | 1.22 (0.93–1.61)  | 0.158     |
|      |          | Recessive | C/C+T/C  | 384 (81.5%)| 451 (80.0%)  | 1              | 1                   | 1                   |           |
|      |          |           | T/T      | 87 (18.5%) | 112 (19.9%)  | 0.91 (0.67–1.25)| 0.564             | 0.93 (0.67–1.28)  | 0.646     |
|      |          | Log-additive| –        | –       | –            | 1.02 (0.86–1.21)| 0.812             | 1.06 (0.89–1.28)  | 0.499     |
| ACYP2| rs1682111 | Codominant| T/T      | 251 (53.3%)| 252 (44.7%)  | 1              | 1                   | 1                   |           |
|      |          |           | A/T      | 181 (38.4%)| 253 (44.9%)  | 0.72 (0.55–0.93)| 0.021*            | 0.69 (0.53–0.91)  | 0.011*    |
|      |          |           | A/A      | 39 (8.3%) | 59 (10.5%)   | 0.66 (0.43–1.03)| 0.62               | 0.62 (0.39–0.98)  |           |
|      |          | Dominant  | T/T      | 251 (53.3%)| 252 (44.7%)  | 1              | 1                   | 1                   |           |
|      |          |           | A/T+A/A  | 220 (46.7%)| 312 (55.4%)  | 0.71 (0.55–0.91)| 0.006*            | 0.68 (0.53–0.88)  | 0.003*    |
|      |          | Recessive | T/T+A/T  | 432 (91.7%)| 505 (89.6%)  | 1              | 1                   | 1                   |           |

(Continued)
| Gene       | SNP        | Model          | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|------------|------------|----------------|----------|-----------|---------------|-----------------|---------------------|
|            |            |                | A/A      | 39 (8.3%) | 59 (10.5%)    | 1.33 (0.92–1.90) | 0.130               |
|            |            |                | Log-additive | –        | –             | 0.77 (0.51–1.18) | 0.234               |
|            |            | Codominant     | T/T      | 232 (49.2%) | 306 (54.4%)   | 1               | 1                   |
|            | rs843752   |                | G/T      | 201 (42.6%) | 214 (38.0%)   | 1.24 (0.96–1.60) | 0.247               |
|            |            |                | G/G      | 39 (8.3%) | 43 (7.6%)     | 1.20 (0.75–1.91) | 1.13 (0.70–1.83)    |
|            |            | Dominant       | T/T      | 232 (49.2%) | 306 (54.4%)   | 1               | 1                   |
| ACYP2      | rs10439478 |                | T/G+G/G  | 240 (50.9%) | 257 (45.6%)   | 1.32 (0.99–1.76) | 0.062               |
|            |            |                | G/G      | 39 (8.3%) | 43 (7.6%)     | 1.09 (0.69–1.71) | 0.711               |
|            |            |                | Log-additive | –        | –             | 1.16 (0.95–1.40) | 0.143               |
|            |            | Codominant     | A/A      | 154 (32.6%) | 206 (36.6%)   | 1               | 1                   |
|            |            |                | C/A      | 233 (49.4%) | 261 (46.4%)   | 1.19 (0.91–1.57) | 0.411               |
|            |            |                | C/C      | 85 (18.0%) | 96 (17.1%)    | 1.18 (0.83–1.70) | 1.31 (0.90–1.90)    |
|            |            | Dominant       | A/A      | 154 (32.6%) | 206 (36.6%)   | 1               | 1                   |
|            |            |                | C/A+C/C  | 318 (67.4%) | 357 (63.5%)   | 1.19 (0.92–1.54) | 0.183               |
|            |            |                | Recessive | A/A+C/A  | 387 (82.0%) | 447 (83.0%)    | 1                   |
|            |            |                | C/C      | 85 (18.0%) | 96 (17.1%)    | 1.07 (0.77–1.47) | 0.687               |
|            |            |                | Log-additive | –        | –             | 1.11 (0.93–1.32) | 0.262               |
|            | rs843645   | Codominant     | T/T      | 235 (49.9%) | 321 (56.9%)   | 1               | 1                   |
|            |            |                | G/T      | 206 (43.7%) | 202 (35.8%)   | 1.39 (1.08–1.80) | 0.035*              |
|            |            |                | G/G      | 30 (6.4%) | 41 (7.3%)     | 1.00 (0.61–1.65) | 0.96 (0.57–1.60)    |
|            |            | Dominant       | T/T      | 235 (49.9%) | 321 (56.9%)   | 1               | 1                   |
|            |            |                | G/T+G/G  | 236 (50.1%) | 243 (43.1%)   | 1.33 (1.04–1.70) | 0.024*              |

(Continued)
| Gene     | SNP      | Model  | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|----------|----------|--------|----------|-----------|---------------|----------------|-------------------|
|          |          |        |          | OR (95% CI) | p             | OR (95% CI)     | p                 |
|          |          | Recessive | T/T + G/T | 441 (93.6%) | 523 (92.7%)  | 1              | 1                 |
|          |          |          | G/G      | 30 (6.4%) | 41 (7.3%) | 0.87 (0.53–1.41) | 0.569 | 0.83 (0.50–1.37) | 0.471 |
|          |          | Log-additive | – | – | – | 1.17 (0.96–1.43) | 0.115 | 1.16 (0.94–1.42) | 0.158 |
| ACYP2    | rs11125529 | Codominant | C/C | 310 (65.7%) | 392 (9.5%) | 1              | 1                 |
|          |          |          | A/C      | 149 (31.6%) | 159 (28.2%) | 1.19 (0.91–1.55) | 0.418 | 1.20 (0.91–1.58) | 0.434 |
|          |          |          | A/A      | 13 (2.8%) | 13 (2.3%) | 1.27 (0.58–2.77) | 0.471 | 1.16 (0.52–2.60) | 0.226 |
|          |          | Dominant | C/C | 310 (65.7%) | 392 (69.5%) | 1              | 1                 |
|          |          |          | A/C + A/A | 162 (34.4%) | 172 (30.5%) | 1.19 (0.92–1.55) | 0.190 | 1.20 (0.91–1.57) | 0.197 |
|          |          | Recessive | C/C + A/C | 459 (97.3%) | 551 (97.7%) | 1              | 1                 |
|          |          |          | A/A      | 13 (2.8%) | 13 (2.3%) | 1.20 (0.55–2.62) | 0.646 | 1.10 (0.49–2.45) | 0.818 |
|          |          | Log-additive | – | – | – | 1.17 (0.93–1.47) | 0.193 | 1.16 (0.91–1.48) | 0.226 |
| ACYP2    | rs12615793 | Codominant | G/G | 297 (62.9%) | 377 (66.8%) | 1              | 1                 |
|          |          |          | A/G      | 160 (33.9%) | 173 (30.7%) | 1.17 (0.90–1.53) | 0.391 | 1.18 (0.90–1.55) | 0.477 |
|          |          |          | A/A      | 15 (3.2%) | 14 (2.5%) | 1.36 (0.65–2.86) | 0.217 | 1.21 (0.56–2.60) | 0.238 |
|          |          | Dominant | G/G | 297 (62.9%) | 377 (66.8%) | 1              | 1                 |
|          |          |          | A/G + A/A | 175 (37.1%) | 187 (33.2%) | 1.19 (0.92–1.54) | 0.188 | 1.18 (0.90–1.54) | 0.224 |
|          |          | Recessive | G/G + A/G | 457 (96.8%) | 550 (97.5%) | 1              | 1                 |
|          |          |          | A/A      | 15 (3.2%) | 14 (2.5%) | 1.29 (0.62–2.70) | 0.500 | 1.15 (0.53–2.45) | 0.728 |
|          |          | Log-additive | – | – | – | 1.17 (0.93–1.47) | 0.171 | 1.15 (0.91–1.46) | 0.238 |
| ACYP2    | rs843711  | Codominant | C/C | 126 (26.8%) | 178 (31.6%) | 1              | 1                 |
|          |          |          | T/C      | 218 (46.3%) | 278 (49.4%) | 1.11 (0.83–1.48) | 0.008* | 1.13 (0.84–1.52) | 0.023* |
|          |          |          | T/T      | 127 (30.0%) | 107 (19.0%) | 1.68 (1.19–2.37) | 0.137 | 1.62 (1.13–2.31) | 0.158 |
|          |          | Dominant | C/C | 126 (26.8%) | 178 (31.6%) | 1              | 1                 |

(Continued)
| Gene | SNP       | Model   | Genotype    | HCC | Control | Crude analysis | Adjustment analysis |
|------|-----------|---------|-------------|-----|---------|----------------|---------------------|
|      |           |         |             | n (%) | n (%)   | OR (95% CI) p  | OR (95% CI) p       |
|      |           |         | T/C + T/T   | 345 (76.3%) | 385 (68.4%) | 1.27 [0.97–1.66] 0.088 | 1.27 [0.96–1.68] 0.095 |
|      |           | Recessive| C/C + T/C   | 344 (73.1%) | 456 (81.0%) | 1 | 1 |
|      |           |         | T/T         | 127 (30.0%) | 107 (19.0%) | 1.57 [1.17–2.11] 0.002* | 1.50 [1.11–2.03] 0.009* |
|      |           |         | Log-additive | – | – | 1.28 [1.08–1.52] 0.004* | 1.26 [1.06–1.51] 0.01* |
|      |           |         |             |       |       |                |                     |
|      |           |         |             |       |       |                |                     |
| ACYP2 | rs11896604| Codominant| C/C         | 288 (61.2%) | 376 (66.7%) | 1 | 1 |
|      |           |         | G/C         | 164 (34.8%) | 167 (29.6%) | 1.28 [0.98–1.67] 0.178 | 1.32 [1.00–1.73] 0.146 |
|      |           |         | G/G         | 19 (4.0%) | 21 (3.7%) | 1.18 [0.62–2.24] 0.587 | 1.08 [0.56–2.08] 0.476 |
|      |           | Dominant | C/C         | 288 (61.2%) | 376 (66.7%) | 1 | 1 |
|      |           |         | G/C + G/G   | 183 (38.8%) | 188 (33.3%) | 1.27 [0.98–1.64] 0.065 | 1.29 [0.99–1.68] 0.061 |
|      |           | Recessive| C/C + G/C   | 452 (96.0%) | 543 (96.3%) | 1 | 1 |
|      |           |         | G/G         | 19 (4.0%) | 21 (3.7%) | 1.09 [0.58–2.05] 0.796 | 0.98 [0.51–1.89] 0.960 |
|      |           |         | Log-additive | – | – | 1.20 [0.97–1.49] 0.097 | 1.20 [0.96–1.50] 0.115 |
|      |           |           |             |       |       |                |                     |
| ACYP2 | rs843706  | Codominant| C/C         | 124 (26.3%) | 177 (31.5%) | 1 | 1 |
|      |           |         | A/C         | 219 (46.5%) | 277 (49.3%) | 1.13 [0.84–1.51] 0.007* | 1.14 [0.84–1.53] 0.024* |
|      |           |         | A/A         | 128 (27.2%) | 108 (19.2%) | 1.69 [1.20–2.39] 1.62 [1.13–2.31] |
|      |           | Dominant | C/C         | 124 (56.3%) | 177 (31.5%) | 1 | 1 |
|      |           |         | A/C + A/A   | 347 (73.7%) | 385 (68.5%) | 1.29 [0.98–1.69] 0.069 | 1.28 [0.96–1.69] 0.090 |
|      |           | Recessive| C/C + A/C   | 343 (72.8%) | 454 (80.8%) | 1 | 1 |
|      |           |         | A/A         | 128 (27.2%) | 108 (19.2%) | 1.57 [1.17–2.10] 0.003* | 1.49 [1.10–2.02] 0.009* |
|      |           |         | Log-additive | – | – | 1.29 [1.09–1.53] 0.004* | 1.26 [1.06–1.51] 0.01* |
|      |           |           |             |       |       |                |                     |
| ACYP2 | rs17045754| Codominant| G/G         | 302 (63.8%) | 390 (69.1%) | 1 | 1 |
|      |           |         | G/C         | 156 (33.0%) | 160 (28.3%) | 1.26 [0.96–1.64] 0.392 | 1.27 [0.97–1.67] 0.076 |
|      |           |         | C/C         | 15 (3.2%) | 14 (2.5%) | 1.38 [0.66–2.91] 1.37 [0.63–2.97] |

(Continued)
| Gene   | SNP     | Model     | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|--------|---------|-----------|----------|-----------|---------------|----------------|---------------------|
|        |         |           |          | n (%)     | OR (95% CI)   | p              | OR (95% CI) p       |
|        |         | Dominant  | G/G      | 302 (63.8%) | 390 (69.1%)   | 1              | 1                   |
|        |         |           | G/C + C/C| 171 (36.2%) | 174 (30.8%)   | 1.27 (0.98–1.64) | 0.071 1.28 (0.88–1.92) | 0.190 |
|        |         | Recessive | G/G + G/C| 458 (96.8%)  | 550 (97.4%)  | 1              | 1                   |
|        |         |           | C/C      | 15 (3.2%)   | 14 (2.5%)     | 1.38 (0.92–2.07) | 0.120 1.27 (0.59–2.74) | 0.536 |
|        |         | Log-additive | –     | –          | –             | 1.29 (0.61–2.69) | 0.504 1.24 (0.97–1.57) | 0.080 |
| ACYP2  | rs843720| Codominant | T/T      | 224 (47.5%) | 242 (42.9%)  | 1              | 1                   |
|        |         |           | G/T      | 210 (44.4%) | 258 (45.7%)  | 0.88 (0.68–1.34) | 0.130 0.85 (0.65–1.11) | 0.134 |
|        |         | Dominant  | T/T      | 224 (47.5%) | 242 (42.9%)  | 1              | 1                   |
|        |         |           | G/T + G/G| 248 (52.5%) | 322 (57.0%)  | 0.83 (0.65–1.06) | 0.143 0.81 (0.63–1.05) | 0.109 |
|        |         | Recessive | T/T + G/T | 434 (91.9%) | 500 (88.6%)  | 1              | 1                   |
|        |         |           | G/G      | 38 (8.1%)  | 64 (11.3%)   | 1.38 (0.92–2.07) | 0.120 0.70 (0.45–1.08) | 0.103 |
|        |         | Log-additive | –     | –          | –             | 0.68 (0.45–1.04) | 0.077 0.82 (0.68–1.00) | 0.049* |
| TERC   | rs35073794| Codominant | G/G     | 463 (98.1%) | 557 (98.7%)  | 1              | 1                   |
|        |         |           | A/G      | 9 (1.9%)   | 7 (1.3%)     | 1              | 1                   |
|        |         |           | A/A      | 0 (0%)     | 0 (0%)       | 1              | 1                   |
|        |         | Dominant  | G/G      | 463 (98.1%) | 557 (98.7%)  | 1              | 1                   |
|        |         |           | A/G + A/A| 9 (1.9%)   | 7 (1.3%)     | 1.55 (0.57–4.19) | 0.390 1.53 (0.55–4.26) | 0.419 |
|        |         | Recessive | G/G + A/A| 472 (100.0%) | 564 (100.0%) | 1              | 1                   |
|        |         |           | A/A      | 0 (0%)     | 0 (0%)       | 0.120          | 0.419               |
|        |         | Log-additive | –     | –          | –             | 1.55 (0.57–4.19) | 0.390 1.53 (0.55–4.26) | 0.419 |
| TERC   | rs10936599| Codominant | T/T     | 134 (28.3%) | 188 (33.3%)  | 1              | 1                   |
|        |         |           | C/T     | 220 (46.5%) | 259 (45.9%)  | 1.19 (0.90–1.59) | 0.117 1.20 (0.89–1.61) | 0.115 |
| Gene SNP | Model | Genotype | Crude analysis | Adjustment analysis |
|---------|-------|----------|----------------|---------------------|
| C/C | 119 (25.2%) | 117 (20.7%) | 1.43 (1.02–2.00) | 1.45 (1.02–2.05) |
| T/T | 134 (28.3%) | 188 (33.3%) | 1 | 1 |
| C/T | 339 (71.7%) | 376 (66.6%) | 1.27 (0.97–1.65) | 0.083 | 1.28 (0.97–1.68) | 0.081 |
| T/T+C/T | 354 (74.8%) | 447 (79.2%) | 1 | 1 |
| C/C | 119 (25.2%) | 117 (20.7%) | 1.28 (0.96–1.72) | 0.092 | 1.30 (0.96–1.75) | 0.091 |
| Log-additive | – | – | – | 1.19 (1.01–1.41) | 0.083 | 1.20 (1.01–1.43) | 0.081 |
| NAF1 rs2320615 | Codominant | G/G | 315 (66.6%) | 346 (61.3%) | 1 | 1 |
| A/G | 146 (30.9%) | 192 (34.0%) | 0.84 (0.64–1.09) | 0.089 | 0.84 (0.64–1.10) | 0.160 |
| A/A | 12 (2.5%) | 26 (4.6%) | 0.51 (0.25–1.02) | 0.056 | 0.56 (0.27–1.15) | 0.112 |
| G/G | 315 (66.6%) | 346 (61.3%) | 1 | 1 |
| A/G+A/A | 158 (33.4%) | 218 (38.6%) | 0.80 (0.62–1.03) | 0.080 | 0.81 (0.62–1.05) | 0.112 |
| G/G+A/G | 461 (97.5%) | 538 (95.3%) | 1 | 1 |
| A/A | 12 (2.5%) | 26 (4.6%) | 0.54 (0.27–1.08) | 0.081 | 0.59 (0.29–1.21) | 0.150 |
| Log-additive | – | – | – | 0.79 (0.63–0.99) | 0.036 | 0.81 (0.64–1.01) | 0.064 |
| TERT rs10069690 | Codominant | C/C | 353 (74.8%) | 386 (68.9%) | 1 | 1 |
| T/C | 111 (23.5%) | 156 (27.9%) | 0.78 (0.59–1.03) | 0.069 | 0.80 (0.60–1.07) | 0.103 |
| T/T | 8 (1.7%) | 18 (3.2%) | 0.49 (0.21–1.13) | 0.48 (0.20–1.15) |
| Dominant | C/C | 353 (74.8%) | 386 (68.9%) | 1 | 1 |
| T/C+T/T | 119 (25.2%) | 174 (31.1%) | 0.75 (0.57–0.98) | 0.038 | 0.77 (0.58–1.02) | 0.067 |
| Recessive | C/C+T/C | 466 (98.3%) | 542 (96.8%) | 1 | 1 |
| T/T | 8 (1.7%) | 18 (3.2%) | 0.52 (0.22–1.21) | 0.127 | 0.51 (0.21–1.21) | 0.126 |
| Log-additive | – | – | – | 0.75 (0.59–0.96) | 0.022 | 0.77 (0.60–0.98) | 0.038 |
| TERT rs2242652 | Codominant | G/G | 355 (75.1%) | 383 (67.9%) | 1 | 1 |

(Continued)
| Gene | SNP                  | Model     | Genotype      | HCC   | Control   | Crude analysis | Adjustment analysis |
|------|----------------------|-----------|---------------|-------|-----------|----------------|---------------------|
|      |                      |           | A/G           | 110 (23.3%) | 160 (28.4%) | 0.74 (0.56–0.98) | 0.018*              |
|      |                      |           | A/A           | 8 (1.6%)    | 21 (3.7%)  | 0.41 (0.18–0.94) | 0.029*              |
|      |                      | Dominant  | G/G           | 355 (75.1%) | 383 (67.9%) | 1              | 1                   |
|      |                      | Dominant  | A/G + A/A     | 118 (24.9%) | 181 (32.1%) | 0.70 (0.54–0.92) | 0.012*              |
|      |                      | Recessive | G/G + A/G     | 465 (98.4%) | 543 (96.3%) | 1              | 1                   |
|      |                      | Recessive | A/A           | 8 (1.6%)    | 21 (3.7%)  | 0.44 (0.20–1.01) | 0.054               |
|      |                      | Log-additive | –     | –          | –           | 0.71 (0.56–0.91) | 0.005*              |
| TERT | rs2853677            | Codominant | A/A           | 183 (38.7%) | 227 (40.2%) | 1              | 1                   |
|      |                      | Codominant | G/A           | 229 (48.5%) | 258 (45.7%) | 1.10 (0.85–1.43) | 0.643               |
|      |                      |            | G/G           | 60 (12.7%)  | 79 (14.1%)  | 0.94 (0.64–1.39) | 0.87 (0.58–1.29)    |
|      |                      | Dominant   | A/A + G/G     | 289 (61.2%) | 337 (59.8%) | 1.06 (0.83–1.37) | 0.628               |
|      |                      | Recessive  | A/A + G/A     | 412 (87.2%) | 485 (85.9%) | 1              | 1                   |
|      |                      |            | G/G           | 60 (12.7%)  | 79 (14.1%)  | 0.89 (0.62–1.28) | 0.543               |
|      |                      | Log-additive | –     | –          | –           | 1.00 (0.84–1.20) | 0.966               |
| TERT | rs2853676            | Codominant | C/C           | 356 (75.4%) | 398 (70.6%) | 1              | 1                   |
|      |                      | Codominant | C/T           | 107 (22.7%) | 153 (27.1%) | 0.78 (0.59–1.04) | 0.217               |
|      |                      |            | T/T           | 9 (1.9%)    | 13 (2.3%)  | 0.77 (0.33–1.83) | 0.68 (0.28–1.65)    |
|      |                      | Dominant   | C/C           | 356 (75.4%) | 398 (70.6%) | 1              | 1                   |
|      |                      |            | C/T + T/T     | 116 (24.6%) | 166 (29.4%) | 0.78 (0.59–1.03) | 0.081               |
|      |                      | Recessive  | C/C + C/T     | 463 (98.1%) | 551 (97.7%) | 1              | 1                   |
|      |                      |            | T/T           | 9 (1.9%)    | 13 (2.3%)  | 0.82 (0.35–1.95) | 0.658               |
|      |                      | Log-additive | –     | –          | –           | 0.81 (0.63–1.04) | 0.093               |

(Continued)
| Gene | SNP    | Model     | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|------|--------|-----------|----------|-----------|---------------|----------------|---------------------|
|      |        |           |          | n (%)     | OR (95% CI)   | p              | OR (95% CI)         | p              |
|      |        |           | T/T      | 414 (87.5%) | 507 (89.9%) | 1.27 (0.86–1.87) | 0.485 | 1.34 (0.90–2.02) | 0.351 |
|      |        |           | T/T      | 414 (87.5%) | 507 (89.9%) | 1             | 1                 |                 |
|      |        |           | C/T      | 58 (12.3%)  | 56 (9.9%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
|      |        |           | C/T+C/C  | 59 (12.5%)  | 57 (10.1%)  | 1.27 (0.86–1.87) | 0.229 | 1.35 (0.90–2.01) | 0.148 |
|      |        |           | T/T+C/T  | 472 (99.8%) | 563 (99.8%) | 1             | 1                 |                 |
|      |        |           | C/C      | 1 (0.2%)   | 1 (0.2%)   | 1.23 (0.08–19.64) | 1.45 (0.08–25.43) |                 |
### Table 3. (Continued)

| Gene | SNP   | Model      | Genotype | HCC n (%) | Control n (%) | Crude analysis | OR (95% CI) | p  | Adjustment analysis | OR (95% CI) | p  |
|------|-------|------------|----------|-----------|---------------|----------------|-------------|----|--------------------|-------------|----|
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            | C/C      | 27 (5.7%) | 22 (3.9%)     | 1.49 (0.84–2.66) | 0.172       |    |                    | 1.33 (0.73–2.41) | 0.354|
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            | Log-additive | –     | –            | 1.23 (1.00–1.52) | 0.050       |    |                    | 1.19 (0.96–1.47) | 0.121|
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            | OBFC1 | rs9325507 | Codominant  | C/C | 216 (45.8%) | 238 (42.2%) | 1 |                | 1 |     |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            | OBFC1 | rs3814220 | Codominant  | A/A | 216 (50.0%) | 238 (42.2%) | 1 |                | 1 |     |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            | OBFC1 | rs12765878 | Codominant | T/T | 218 (46.1%) | 238 (42.2%) | 1 |                | 1 |     |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |
|      |       |            |          |           |               |                |             |    |                    |             |    |

(Continued)
### Table 3. (Continued)

| Gene      | SNP          | Model      | Genotype | HCC       | Control    | Crude analysis | Adjustment analysis |
|-----------|--------------|------------|----------|-----------|------------|----------------|---------------------|
|           |              |            |          | n (%)     | n (%)      | OR (95% CI)    | p                   | OR (95% CI)        | p                 |
|           |              |            | Recessive| T/T + C/T | 431 (91.1%)| 509 (90.2%) | 1                 | 1                   | 1                 |
|           |              |            | C/C      | 42 (8.9%) | 55 (9.8%)  | 0.90 (0.59–1.38)| 0.631              | 0.88 (0.57–1.36)   | 0.561              |
|           |              |            | Log-additive| –         | –         | 0.89 (0.74–1.08)| 0.235              | 0.89 (0.73–1.08)   | 0.224              |
| OBFC1     | rs11191865   | Codominant | G/G      | 217 (45.9%)| 238 (42.2%)| 1                 | 1                   | 1                 |
|           |              |            | A/G      | 214 (45.2%)| 271 (48.0%)| 0.86 (0.66–1.11)| 0.450              | 0.87 (0.67–1.13)   | 0.493              |
|           |              |            | A/A      | 42 (8.9%)  | 55 (9.8%)  | 0.83 (0.54–1.30)| 1.235              | 0.82 (0.52–1.29)   | 0.82               |
|           |              |            | Dominant | G/G      | 217 (45.9%)| 238 (42.2%) | 1                 | 1                   | 1                 |
|           |              |            | A/G + A/A| 256 (54.1%)| 326 (57.8%)| 0.85 (0.67–1.09)| 0.209              | 0.86 (0.67–1.11)   | 0.246              |
|           |              |            | Recessive| G/G + A/G | 431 (91.1%)| 509 (90.2%) | 1                 | 1                   | 1                 |
|           |              |            | A/A      | 42 (8.9%)  | 55 (9.8%)  | 0.90 (0.59–1.38)| 0.631              | 0.88 (0.57–1.36)   | 0.561              |
|           |              |            | Log-additive| –         | –         | 0.89 (0.74–1.08)| 0.235              | 0.89 (0.73–1.08)   | 0.224              |
| OBFC1     | rs9420907    | Codominant | A/A      | 463 (97.9%)| 551 (98.0%)| 1                 | 1                   | 1                 |
|           |              |            | C/A      | 10 (21.1%) | 11 (20.0%) | /                 | /                   | /                 |
|           |              |            | C/C      | 10 (21.1%) | 11 (20.0%) | /                 | /                   | /                 |
|           |              |            | Dominant | A/A      | 463 (97.9%)| 551 (98.0%) | 1                 | 1                   | 1                 |
|           |              |            | C/A + C/C| 10 (21.1%) | 11 (20.0%) | 1.08 (0.46–2.57)| 0.859              | 0.90 (0.37–2.17)   | 0.808              |
|           |              |            | Recessive| A/A + C/A | 473 (100.0%)| 562 (100.0%)| 1                 | 1                   | 1                 |
|           |              |            | C/C      | 0 (0%)    | 0 (0%)     | /                 | /                   | /                 |
|           |              |            | Log-additive| –         | –         | 1.08 (0.46–2.57)| 0.859              | 0.90 (0.37–2.17)   | 0.808              |
| MPHOSPH6  | rs1056675    | Codominant | T/T      | 160 (34.1%)| 202 (35.9%)| 1                 | 1                   | 1                 |
|           |              |            | C/T      | 224 (47.6%)| 274 (48.8%)| 1.03 (0.79–1.36)| 0.427              | 1.02 (0.77–1.36)   | 0.442              |
|           |              |            | C/C      | 86 (18.3%) | 86 (15.3%) | 1.26 (0.88–1.82)| 1.26 (0.87–1.84)   | 1.26 (0.87–1.84)   | 0.88               |
|           |              |            | Dominant | T/T      | 160 (34.1%)| 202 (35.9%) | 1                 | 1                   | 1                 |

(Continued)
| Gene  | SNP       | Model     | Genotype | HCC       | Control   | Crude analysis | Adjustment analysis |
|-------|-----------|-----------|----------|-----------|-----------|----------------|---------------------|
|       |           |           |          | n (%)     | n (%)     | OR (95% CI)    | p                   |
|       |           |           |          | n (%)     | n (%)     | OR (95% CI)    | p                   |
|       |           |           |          | OR (95% CI) | p         | OR (95% CI)    | p                   |
|       |           |           |          | p         |           | p                   |

**MPHOSPH6 rs1056654**

| Genotype | HCC | Control |
|----------|-----|---------|
| C/T + C/C | 310 (65.9%) | 360 (64.1%) |
| T/T + C/T | 384 (81.7%) | 476 (84.7%) |
| C/C | 86 (18.3%) | 86 (15.3%) |
| Log-additive | – | – |

**MPHOSPH6 rs3751862**

| Genotype | HCC | Control |
|----------|-----|---------|
| A/A | 417 (88.2%) | 499 (88.6%) |
| C/A | 56 (11.8%) | 63 (11.2%) |
| C/C | 0 (0.0%) | 1 (0.2%) |
| Log-additive | – | – |

(Continued)
| Gene    | SNP        | Model       | Genotype | HCC   | Control | Crude analysis | Adjusted analysis |
|---------|------------|-------------|----------|-------|---------|----------------|--------------------|
|         |            |             |          | n (%) | n (%)   | OR (95% CI)    | p                  |
| MPHOSPH6 | rs11859599 | Codominant  | G/G      | 306 (64.8%) | 364 (64.5%) | 1               | 1                  |
|         |            |             | C/G      | 142 (30.1%) | 167 (29.6%) | 1.01 (0.77–1.33) | 0.862 | 1.09 (0.82–1.44) | 0.651 |
|         |            |             | C/C      | 24 (5.1%) | 33 (5.9%) | 0.87 (0.50–1.50) | 0.84 (0.47–1.47) |
|         |            | Dominant    | G/G      | 306 (64.8%) | 364 (64.5%) | 1               | 1                  |
|         |            |             | C/G      | 166 (35.2%) | 200 (35.5%) | 0.99 (0.76–1.28) | 0.922 | 1.04 (0.80–1.36) | 0.755 |
|         |            |             | C/C      | 24 (5.1%) | 33 (5.9%) | 0.86 (0.50–1.48) | 0.590 | 0.81 (0.47–1.42) | 0.471 |
|         |            | Recessive   | G/G      | 448 (94.9%) | 531 (94.1%) | 1               | 1                  |
|         |            |             | C/C      | 24 (5.1%) | 33 (5.9%) | 0.86 (0.50–1.48) | 0.590 | 0.81 (0.47–1.42) | 0.471 |
|         |            | Log-additive | –        | –     | –     | 0.97 (0.79–1.19) | 0.775 | 1.00 (0.80–1.23) | 0.979 |
| MPHOSPH6 | rs2967361  | Codominant  | G/G      | 276 (58.4%) | 346 (61.6%) | 1               | 1                  |
|         |            |             | T/G      | 173 (36.6%) | 180 (32.0%) | 1.21 (0.93–1.57) | 0.249 | 1.26 (0.96–1.65) | 0.151 |
|         |            |             | T/T      | 24 (5.0%) | 36 (6.4%) | 0.84 (0.49–1.43) | 0.81 (0.46–1.42) |
|         |            | Dominant    | G/G      | 276 (58.4%) | 346 (61.6%) | 1               | 1                  |
|         |            |             | T/G      | 197 (41.6%) | 216 (38.4%) | 1.14 (0.89–1.47) | 0.293 | 1.18 (0.91–1.53) | 0.212 |
|         |            | Recessive   | G/G      | 449 (95.0%) | 526 (93.6%) | 1               | 1                  |
|         |            |             | G/G      | 24 (5.0%) | 36 (6.4%) | 0.78 (0.46–1.33) | 0.362 | 0.75 (0.43–1.30) | 0.300 |
|         |            | Log-additive | –        | –     | –     | 1.05 (0.86–1.29) | 0.617 | 1.07 (0.87–1.32) | 0.541 |
| ZNF208  | rs2188972  | Codominant  | G/G      | 111 (23.5%) | 150 (24.8%) | 1               | 1                  |
|         |            |             | A/G      | 241 (50.9%) | 274 (48.6%) | 1.19 (0.88–1.61) | 0.510 | 1.21 (0.88–1.65) | 0.486 |
|         |            |             | A/A      | 121 (25.6%) | 140 (24.8%) | 1.17 (0.83–1.65) | 1.17 (0.82–1.68) |
|         |            | Dominant    | G/G      | 111 (23.5%) | 150 (24.8%) | 1               | 1                  |
|         |            |             | A/G      | 362 (76.5%) | 414 (73.4%) | 1.18 (0.89–1.57) | 0.248 | 1.20 (0.89–1.60) | 0.235 |
|         |            | Recessive   | G/G      | 352 (74.4%) | 424 (73.4%) | 1               | 1                  |
|         |            |             | A/A      | 121 (25.6%) | 140 (24.8%) | 1.04 (0.79–1.38) | 0.779 | 1.04 (0.77–1.39) | 0.816 |
| Gene | SNP      | Model       | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjusted analysis |
|------|----------|-------------|----------|-----------|---------------|----------------|-------------------|
|      |          |             |          | n (%)     |               |                |                   |
|      |          |             |          | n (%)     |               |                |                   |
|      |          |             |          | OR (95% CI) | p       | OR (95% CI) | p       |
|      |          |             |          | Log-additive | –        | –        | –        | 1.08 (0.91–1.28)  | 0.380 | 1.08 (0.91–1.29)  | 0.385 |
|      |          | Codominant  | C/C      | 229 (48.5%) | 288 (51.2%) | 1               | 1.08 (0.91–1.29)  | 0.385 |
|      |          |             | T/C      | 199 (42.2%) | 224 (39.8%) | 1.12 (0.86–1.45) | 0.694 | 1.22 (0.93–1.59)  | 0.326 |
|      |          |             | T/T      | 44 (9.3%) | 51 (10.0%) | 1.09 (0.70–1.68) | 1.21 (0.77–1.92) |
|      |          | Dominant    | C/C      | 229 (48.5%) | 288 (51.2%) | 1               | 1.08 (0.91–1.29)  | 0.385 |
|      |          |             | T/C + T/T | 243 (51.5%) | 275 (49.8%) | 1.11 (0.87–1.42) | 0.398 | 1.22 (0.94–1.57)  | 0.134 |
|      |          |             |          |            |               |                |                   |
|      |          | Recessive   | C/C + T/C | 428 (90.7%) | 512 (91.0%) | 1               | 1.15 (0.94–1.39)  | 0.175 |
|      |          |             | T/T      | 44 (9.3%) | 51 (10.0%) | 1.07 (0.89–1.29) | 0.476 | 1.15 (0.94–1.39)  | 0.175 |
|      |          | Log-additive| –        | –        | –        | 1.07 (0.89–1.29) | 0.476 | 1.15 (0.94–1.39)  | 0.175 |
|      |          | Codominant  | C/C      | 228 (48.4%) | 288 (51.1%) | 1               | 1.22 (0.93–1.59)  | 0.317 |
|      |          |             | A/C      | 199 (42.3%) | 225 (39.9%) | 1.12 (0.86–1.45) | 0.692 | 1.22 (0.93–1.59)  | 0.317 |
|      |          |             | A/A      | 44 (9.3%) | 51 (9.0%) | 1.09 (0.70–1.69) | 1.23 (0.78–1.94) |
|      |          | Dominant    | C/C      | 228 (48.4%) | 288 (51.1%) | 1               | 1.22 (0.94–1.57)  | 0.130 |
|      |          |             | C/C + A/C | 243 (51.6%) | 276 (48.9%) | 1.11 (0.87–1.42) | 0.395 | 1.22 (0.94–1.57)  | 0.130 |
|      |          | Recessive   | A/C + A/A | 431 (90.7%) | 513 (91.0%) | 1               | 1.15 (0.94–1.40)  | 0.166 |
|      |          |             | A/A      | 44 (9.3%) | 51 (9.0%) | 1.04 (0.68–1.58) | 0.868 | 1.12 (0.72–1.74)  | 0.616 |
|      |          | Log-additive| –        | –        | –        | 1.07 (0.89–1.29) | 0.468 | 1.15 (0.94–1.40)  | 0.166 |
|      |          | Codominant  | C/C      | 231 (48.9%) | 288 (51.1%) | 1               | 1.18 (0.90–1.55)  | 0.385 |
|      |          |             | A/C      | 196 (41.4%) | 224 (39.7%) | 1.09 (0.84–1.41) | 0.774 | 1.18 (0.90–1.55)  | 0.385 |
|      |          |             | A/A      | 46 (9.7%) | 52 (9.2%) | 1.10 (0.72–1.70) | 1.24 (0.79–1.95) |
|      |          | Dominant    | C/C      | 231 (48.9%) | 288 (51.1%) | 1               | 1.18 (0.90–1.55)  | 0.385 |
|      |          |             | C/C + A/C | 242 (51.1%) | 276 (48.9%) | 1.09 (0.86–1.40) | 0.475 | 1.19 (0.93–1.54)  | 0.172 |
|      |          | Recessive   | A/C + A/A | 427 (90.3%) | 512 (90.8%) | 1               | 1.19 (0.93–1.54)  | 0.172 |
| Gene | SNP   | Model       | Genotype | HCC n (%) | Control n (%) | Crude analysis | Adjustment analysis |
|------|-------|-------------|----------|-----------|---------------|----------------|---------------------|
|      |       |             | A/A      | 46 (9.7%) | 52 (9.2%)     | 1.06 (0.70–1.61)| 1.15 (0.75–1.77)  |
|      |       |             | Log-additive | –        | –             | 1.07 (0.89–1.28)| 1.14 (0.94–1.39)  |
|      |       |             | ZNF208 rs8105767 | Codominant | A/A | 226 (47.9%) | 272 (48.6%) | 1.07 (0.89–1.28) | 0.93 (0.72–1.22) | 0.861 |
|      |       |             | G/A      | 205 (43.4%) | 242 (43.2%) | 1.02 (0.79–1.32) | 1.02 (0.64–1.64) |
|      |       |             | G/G      | 41 (8.7%) | 46 (8.2%) | 1.07 (0.68–1.70) | 1.07 (0.68–1.70) |
|      |       |             | Dominant | A/A      | 226 (47.9%) | 272 (48.6%) | 1.07 (0.89–1.28) | 0.93 (0.72–1.22) | 0.861 |
|      |       |             | G/A      | 205 (43.4%) | 242 (43.2%) | 1.02 (0.79–1.32) | 1.02 (0.64–1.64) |
|      |       |             | G/G      | 41 (8.7%) | 46 (8.2%) | 1.07 (0.68–1.70) | 1.07 (0.68–1.70) |
|      |       |             | RTEL1 rs6089953 | Codominant | A/A | 241 (50.9%) | 289 (51.3%) | 1.07 (0.89–1.28) | 1.07 (0.89–1.28) | 0.861 |
|      |       |             | G/A      | 188 (39.7%) | 224 (39.8%) | 1.01 (0.78–1.30) | 1.01 (0.78–1.30) |
|      |       |             | G/G      | 44 (9.3%) | 50 (8.9%) | 1.06 (0.68–1.64) | 1.06 (0.68–1.64) |
|      |       |             | Dominant | A/A      | 241 (50.9%) | 289 (51.3%) | 1.07 (0.89–1.28) | 1.07 (0.89–1.28) | 0.861 |
|      |       |             | G/A      | 188 (39.7%) | 224 (39.8%) | 1.01 (0.78–1.30) | 1.01 (0.78–1.30) |
|      |       |             | G/G      | 44 (9.3%) | 50 (8.9%) | 1.06 (0.68–1.64) | 1.06 (0.68–1.64) |
|      |       |             | RTEL1 rs6010621 | Codominant | T/T | 259 (55.0%) | 298 (52.9%) | 1.02 (0.84–1.23) | 1.02 (0.84–1.23) | 0.627 |
|      |       |             | G/T      | 176 (37.4%) | 222 (39.4%) | 0.91 (0.70–1.18) | 0.90 (0.69–1.17) |
|      |       |             | G/G      | 36 (7.6%) | 43 (7.6%) | 0.96 (0.60–1.55) | 0.96 (0.60–1.55) |
|      |       |             | Dominant | T/T      | 259 (55.0%) | 298 (52.9%) | 1.02 (0.84–1.23) | 1.02 (0.84–1.23) | 0.627 |
|      |       |             | G/T      | 176 (37.4%) | 222 (39.4%) | 0.91 (0.70–1.18) | 0.90 (0.69–1.17) |
|      |       |             | G/G      | 36 (7.6%) | 43 (7.6%) | 0.96 (0.60–1.55) | 0.96 (0.60–1.55) |
|      |       |             | (Continued) |          |             |                |                  |
| Gene | SNP   | Model     | Genotype | HCC  | Control | Crude analysis | Adjustment analysis |
|------|-------|-----------|----------|------|---------|----------------|---------------------|
|      |       |           |          | n (%)| n (%)   | OR (95% CI)    | p       | OR (95% CI)    | p       |
|      |       | Recessive | T/T + G/T| 435  | 520     | 1             | 1       | 1.13 (0.70–1.83) | 0.620   |
|      |       |           | G/G      | 36   | 43      | 1.00 (0.63–1.59) | 0.997   | 0.97 (0.79–1.19) | 0.777   |
|      |       | Log-additive | –       | –    | –       | 0.95 (0.78–1.15) | 0.604   | –               | –       |
| RTEL1| rs4809324 | Codominant | T/T     | 355  | 440     | 1             | 1       | 1.18 (0.87–1.61) | 0.324   |
|      |       |           | C/T     | 107  | 115     | 1.15 (0.86–1.55) | 0.534   | 1.18 (0.87–1.61) | 0.324   |
|      |       |           | C/C     | 9    | 8       | 1.39 (0.53–3.65) | 0.620   | 1.60 (0.65–4.94) | 0.172   |
|      |       | Recessive | T/T + C/T| 462  | 555     | 1             | 1       | 1.35 (0.52–3.53) | 0.324   |
|      |       |           | C/C     | 9    | 8       | 1.06 (0.70–1.61) | 0.534   | 1.25 (0.94–1.91) | 0.324   |
|      |       | Log-additive | –       | –    | –       | 1.35 (0.52–3.53) | 0.534   | –               | –       |
| RTEL1| rs2297441 | Codominant | G/G    | 224  | 257     | 1             | 1       | 1.90 (0.66–1.13) | 0.194   |
|      |       |           | A/G     | 190  | 251     | 0.87 (0.67–1.13) | 0.246   | 0.86 (0.66–1.13) | 0.194   |
|      |       |           | A/A     | 224  | 56      | 1.21 (0.80–1.82) | 0.217   | 1.25 (0.82–1.91) | 0.194   |
|      |       | Dominant  | G/G     | 224  | 257     | 1             | 1       | 1.05 (0.86–1.33) | 0.607   |
|      |       |           | A/G + A/A| 414  | 307     | 0.93 (0.73–1.19) | 0.565   | 0.93 (0.72–1.20) | 0.575   |
|      |       | Recessive | G/G + A/G| 414  | 508     | 1             | 1       | 1.35 (0.90–2.01) | 0.149   |
|      |       |           | A/A     | 224  | 56      | 1.29 (0.88–1.91) | 0.195   | 1.35 (0.90–2.01) | 0.149   |
|      |       | Log-additive | –       | –    | –       | 1.02 (0.85–1.22) | 0.857   | 1.03 (0.85–1.24) | 0.795   |

CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio; SNP, single nucleotide polymorphism. *p < 0.05.
Figure 3. Linkage disequilibrium between the two SNPs.

(a) Haplotype block map for all the SNPs of the ACYP2 on chromosome 2. (b) Haplotype block map for the two SNPs of the TERC on chromosome 3. (c) Haplotype block map for all the SNPs of TERT on chromosome 5. (d) Haplotype block map for all the SNPs of TNIP1 on chromosome 5. (e) Haplotype block map for all the SNPs of OBFC1 on chromosome 10. (f) Haplotype block map for all the SNPs of MPHOSPH6 on chromosome 16. (g) Haplotype block map for all the SNPs of ZNF208 on chromosome 19. (h) Haplotype block map for all the SNPs of RTEL1 on chromosome 20.

SNP, single nucleotide polymorphism.
Table 4. The correlation between the haplotype frequency and the risk of HCC.

| Gene   | SNP               | Haplotype | Frequency | Crude analysis | p       | Adjusted analysis | p       |
|--------|-------------------|-----------|-----------|----------------|---------|-------------------|---------|
|        |                   |           |           | OR (95% CI)    |         | OR (95% CI)       |         |
|        |                   |           |           | p              |         | p                 |         |
|        |                   | ACATCGCC  | 0.2754    | 0.76 [0.62–0.92] | 0.006* | 0.76 [0.62–0.92] | 0.006* |
|        |                   | TTCTAATG  | 0.1879    | 1.18 [0.93–1.51] | 0.176  | 1.18 [0.93–1.51] | 0.176  |
|        |                   | TGAGCGTC  | 0.2711    | 1.12 [0.91–1.38] | 0.288  | 1.12 [0.91–1.38] | 0.288  |
|        |                   | TTCTCGCC  | 0.1922    | 1.02 [0.81–1.28] | 0.851  | 1.02 [0.81–1.28] | 0.851  |
|        |                   | TTCTCGTG  | 0.014     | 1.19 [0.53–2.67] | 0.677  | 1.19 [0.53–2.67] | 0.677  |
|        |                   | TTCTCACC  | 0.013     | 0.81 [0.38–1.72] | 0.587  | 0.81 [0.38–1.72] | 0.587  |
|        |                   | AC       | 0.19      | 1.21 [0.96–1.53] | 0.100  | 1.22 [0.96–1.55] | 0.107  |
|        |                   | AG       | 0.3142    | 1.20 [1.00–1.46] | 0.055  | 1.17 [0.96–1.43] | 0.115  |
|        |                   | CG       | 0.4894    | 0.76 [0.64–0.91] | 0.002* | 0.78 [0.65–0.93] | 0.006* |
|        |                   | TA       | 0.1282    | 0.75 [0.59–0.96] | 0.020* | 0.77 [0.60–0.99] | 0.040* |
|        |                   | CG       | 0.8602    | 1.38 [1.08–1.75] | 0.009* | 1.37 [1.07–1.75] | 0.013* |
|        |                   | GC       | 0.2468    | 1.25 [1.01–1.54] | 0.039* | 1.20 [0.96–1.48] | 0.108  |
|        |                   | CT       | 0.7532    | 0.81 [0.66–1.00] | 0.050  | 0.84 [0.68–1.05] | 0.121  |
|        |                   | TCGA     | 0.3142    | 0.90 [0.74–1.08] | 0.258  | 0.89 [0.73–1.09] | 0.254  |
|        |                   | CATC     | 0.6815    | 1.10 [0.91–1.33] | 0.338  | 1.11 [0.91–1.35] | 0.316  |
|        |                   | TGCT     | 0.0593    | 1.08 [0.74–1.58] | 0.685  | 1.11 [0.75–1.64] | 0.616  |
|        |                   | TGAT     | 0.1695    | 1.03 [0.82–1.28] | 0.829  | 1.04 [0.82–1.30] | 0.770  |
|        |                   | TAAG     | 0.3167    | 0.90 [0.75–1.09] | 0.273  | 0.89 [0.73–1.07] | 0.209  |
|        |                   | CGAG     | 0.4184    | 1.10 [0.92–1.31] | 0.294  | 1.10 [0.91–1.32] | 0.325  |
|        |                   | TGAG     | 0.0318    | 0.82 [0.52–1.32] | 0.428  | 0.89 [0.55–1.46] | 0.648  |
|        |                   | ATAA     | 0.303     | 1.07 [0.89–1.30] | 0.464  | 1.15 [0.94–1.39] | 0.175  |
|        |                   | GCCC     | 0.4873    | 0.93 [0.78–1.10] | 0.394  | 0.92 [0.77–1.10] | 0.385  |
|        |                   | ACCC     | 0.2055    | 1.02 [0.82–1.26] | 0.887  | 0.94 [0.75–1.17] | 0.569  |
|        |                   | GGC      | 0.1255    | 1.15 [0.88–1.50] | 0.312  | 1.20 [0.91–1.59] | 0.188  |
|        |                   | GGT      | 0.1319    | 0.82 [0.64–1.05] | 0.118  | 0.82 [0.63–1.06] | 0.123  |
|        |                   | GTT      | 0.033     | 1.67 [0.97–2.88] | 0.064  | 1.79 [1.02–3.14] | 0.044* |
|        |                   | ATT      | 0.7021    | 0.99 [0.82–1.19] | 0.917  | 0.96 [0.79–1.16] | 0.667  |

CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio; SNP, single nucleotide polymorphism.
*p < 0.05.
0.62–0.92, \( p=0.006 \)), the haplotype ‘CG’ in the \( \text{TERT} \) gene (OR=0.78, 95% CI: 0.65–0.93, \( p=0.006 \)), and the haplotype ‘TA’ in the \( \text{TERT} \) gene (OR=0.77, 95% CI: 0.60–0.99, \( p=0.040 \)) decreased the risk of HCC.

**Discussion**

Due to its high morbidity and mortality, HCC seriously threatens human health and represents a significant medical burden worldwide. China has more than half of the world’s new cases of liver cancer every year.\(^{31} \) However, the lack of effective early screening and diagnosis of liver cancer leads to ineffective treatment and poor prognosis. Thus, it is necessary to explore novel and potential useful methods and biomarkers for early diagnosis and treatment of liver cancer.

In this study, 42 candidate SNP sites were closely associated with the occurrence of liver cancer as assessed by gene screening. Briefly, the SNP sites were distributed in nine telomere-related genes including \( \text{ACYP2, TERC, NAF1, TERT, TNIP1, OBFC1, MPHOSPH6, ZNF208} \) and \( \text{RTEL1} \).

**1. ACYP2 gene polymorphisms**

The \( \text{ACYP2} \) gene encodes acylphosphatase and regulates different physiological behaviors such as the glycolysis pathway, pyruvate metabolism and cell apoptosis.\(^{14} \) It also has biological functions affecting telomere length. Previous studies reported that the \( \text{ACYP2} \) gene was associated with leukocyte telomere length, and its polymorphisms are associated with lung disease risk in the Han Chinese population.\(^{32} \) The \( \text{ACYP2} \) rs1872328 mutant is potentially related to the toxicity induced by cisplatin chemotherapy in patients with osteosarcoma and could be used to identify patients who should receive cisplatin chemotherapy.\(^{33} \) Acylphosphatase encoded by the \( \text{ACYP2} \) gene is also associated with cell differentiation, cell senescence and cell apoptosis.\(^{34} \) It regulates intracellular \( \text{Ca}^{2+} \) homeostasis.\(^{14} \) Dysregulation of the \( \text{ACYP2} \) gene leads to cell apoptosis.\(^{35} \) Cancer cells prevented \( \text{Ca}^{2+} \) influx by altering cell membrane receptors and reducing the expression of \( \text{Ca}^{2+} \) channels,\(^{36} \) thereby achieving resistance to long-term endoplasmic reticulum calcium deficiency and downregulating mitochondrial calcium one-way transporters and subsequently escaping apoptosis.\(^{37} \) Thus, mutations in the \( \text{ACYP2} \) gene may modulate apoptosis and promote tumor development. Current studies reported that \( \text{ACYP2} \) gene polymorphisms were associated with stroke,\(^{38} \) lung cancer,\(^{32} \) esophageal cancer,\(^{39} \) breast cancer\(^{40} \) and gastric cancer.\(^{41} \) In this study, the ‘G’ allele of rs6713088 in the \( \text{ACYP2} \) gene, was distributed in 45.2% of patients with HCC and 39.3% of healthy individuals, revealing a statistically significant association with HCC risk (OR=1.27, 95% CI=1.07–1.52, \( p=0.007 \)). Based on the genotype frequency distribution, the ‘G/C+G/G’ genotype was associated with increased HCC risk (OR=1.32, 95% CI=1.01–1.74, \( p=0.043 \)) in the dominant model. This site also affects the susceptibility of the Chinese Han population to increased lung edema at high altitude.\(^{42} \) Another ‘A/T’ genotype of rs1682111 was associated with reduced HCC risk (OR=0.69, 95% CI=0.53–0.91, \( p=0.011 \)) in the Chinese Han population.

**2. TERC gene polymorphisms**

The \( \text{TERT} \) gene is found on chromosome 3q26, contains a sequence that is complementary to telomeres and could be used as a template for telomere repeats, and encodes telomerase RNA. This gene maintains telomere length by adding ‘TTAGGG’ repeats to telomere ends. Telomerase plays an important role in cell senescence, and its degradation in somatic cells may also lead to cancer. Montanaro \textit{et al.}\(^{43} \) reported decreased expression of keratins along with low \( \text{TERT} \) gene expression in patients with primary breast cancer, which further affects telomerase activity. Furthermore, lentivirus transfection to induce high expression of the \( \text{TERT} \) gene could eliminate telomerase damage caused by keratin reduction. Flacco \textit{et al.} evaluated the correlation between genomic imbalance and clinicopathological parameters and prognosis by exploring copy number changes in the \( \text{TERT} \) gene in patients with early non-small cell lung cancer and found that the increased \( \text{TERT} \) gene copy number significantly affected histopathological changes in the lungs of patients.\(^{44} \) These findings highlighted the importance of \( \text{TERT} \) gene in maintaining telomerase activity. This study found that the ‘C’ allele of rs10936599 located in the promoter region of \( \text{TERT} \) gene was associated with a statistically significant reduction in HCC risk (OR=1.21, 95% CI=1.02–1.44, \( p=0.032 \)). Genotype frequency distribution and additive model correction analysis confirmed that \( \text{TERT} \) gene was involved in increased susceptibility to liver cancer. This finding is potentially attributed to the fact that gene
polymorphism in the promoter region changed telomerase activity by affecting TERC gene copy number and expression.

3. NAF1 gene polymorphisms

The NAF1 gene, which can be replaced by NOL1/GAR1 in protein particles assembly, enabled the generation of mature ribosomal protein particles and affects telomerase synthesis and activity.45 SNPs located in this gene region (4q32.2) affect telomere length and play an important role as potential susceptibility sites in telomerase activity and cancer development in colorectal cancer patients.15 In this study, the rs2320615 ‘A’ allele located in the intron region of the NAF1 gene was associated with reduced risk of HCC (OR = 0.79, 95% CI = 0.64–0.99, p = 0.038). Based on genotype frequency distribution analysis, this site was still associated with reduced susceptibility in the additive model (OR = 0.79, 95% CI = 0.63–0.99, p = 0.036).

4. TERT gene polymorphisms

The TERT gene regulates telomere extension based on its catalytic properties. TERT also interacts and combines with other proteins to modulate the formation and subcellular localization of telomerase.45 TERT gene expression levels significantly affect telomerase activity in various cells and tissues. The TERT gene is involved in the occurrence and development of various diseases, including congenital dyskeratosis,46 aplastic anemia,47 bone marrow failure syndrome48 and pulmonary fibrosis.49 In addition, TERT gene polymorphisms are also involved in the pathogenesis of a variety of tumors. The functional repeat small satellite sequence polymorphism of TERT affects the prognosis of patients with non-small cell lung cancer.50 The rs2242652 SNP located in the intron region of TERT gene was associated with shortened telomere length and significantly affects the risk of prostate cancer.51 In breast cancer, alleles rs2736109 ‘G’ (OR = 1.56, 95% CI = 1.22–1.99) and rs3816659 ‘T’ (OR = 1.27, 95% CI = 1.05–1.52) located in the TERT gene also increase the risk of breast cancer compared with the healthy population. The above studies suggested that TERT gene polymorphisms play an important role in the pathogenesis of cancer. In our study, TERT gene polymorphism sites rs10069690 and rs2242652 could affect the risk of HCC in the Chinese Han population. This study provided new insights into the development of HCC that may have important clinical application value in screening and early diagnosis in high-risk HCC populations.

Multiple studies showed that SNPs and gene variations could result in the occurrence and development of HCC. In the present study, a total of five loci were significantly associated with a high risk of HCC. Based on the genotype distribution, rs6713088, rs843645, rs843711 and rs843706 located in the ACYP2 gene and rs10936599 located in the TERT gene were obviously associated with a high risk of HCC. In addition, SNPs in these genes could form a linkage imbalance haplotype. Specifically, the haploid ‘GC’ formed by rs10069690 and rs2242652 within the TERT gene increased the risk of HCC. The results suggested that the SNPs in these genes could influence telomere length and may play a key role in the occurrence and progression of HCC. The results revealed that some specific gene site alterations might be associated with HCC. This study also provided more insights into the pathogenic mechanism and early detection of HCC. Of note, we attributed the significant differences among dominant, codominant and additive models to the following reasons: (1) the deviation was caused by the large proportion of heterozygotes G/T in these three genotypes; (2) the population sample size was small, causing statistical deviation; and (3) sex and age mismatch between case and control groups may also explain these findings.

We identified polymorphisms in telomere length-related genes, and SNPs in some gene loci correlated with high HCC risk. However, the functions and the precise mechanism of gene variability were not extensively investigated. We do not exactly understand how environment factors and other gene mutations alone or in combination could impact the results. Therefore, research and studies in liver cancer cell lines and animal HCC models are required to clarify the above gene functions in HCC. Further studies are needed to assess whether these gene variation will support our findings. In our study, we found that some gene loci were associated with HCC risk, but whether mutations in these loci could predict the prognosis of HCC remains unknown. We will continue to track the prognosis of these patients for further analysis in future studies. Some limitations in our study should be noted. First, the sample size of the population was relatively small. Second, all of these volunteers were recruited...
from Xi’an, Shaanxi province. More samples from different areas are therefore needed for analysis. Third, this study lacked complete detailed clinical information (such as smoking, drinking, and hepatitis C virus infection) in all volunteers; only age and gender were recorded. We need to collect sufficient information on the clinical characteristic of participants to obtain more data and valuable results in the future studies. Finally, telomere shortening is a common phenomenon in human cancers, including HCC; however, we did not investigate whether the presence of these SNPs influences telomere length in this cohort of patients.

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**Conflict of interest statement**

The authors declare that there is no conflict of interest.

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**Data availability**

The data used to support the findings of this study are included within the article.

**Supplemental material**

Supplemental material for this article is available online.

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