Research Article

**MIR17HG** polymorphism (rs7318578) is associated with liver cancer risk in the Chinese Han population

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Numerous evidence has revealed that single-nucleotide polymorphisms (SNPs) are associated with liver cancer risk. To assess whether the MIR17HG polymorphisms are associated with the liver cancer risk in the Chinese Han population, we performed a case–control (432 liver cancer patients and 430 healthy controls) study. Genotyping of four variants of MIR17HG was performed with the Agena MassARRAY platform. We used \( \chi^2 \) test to compare the distribution of SNPs allele and genotypes frequencies of cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression analysis to evaluate the association under genetic models. The results indicated that the rs7318578 was significantly associated with increased the risk of liver cancer in the allele (OR = 1.45, 95% CI: 1.18–1.77, \( P = 3.04E-04 \)), recessive (OR = 3.69, 95% CI: 2.45–5.56, \( P = 4.52E-10 \)) and additive model (OR = 1.35, 95% CI: 1.13–1.62, \( P = 0.001 \)). Moreover, we found that individuals with the genotype CC of rs7318578 presented with an increased risk of liver cancer (OR = 3.03, 95% CI: 1.98–4.65, \( P = 3.83E-07 \)); however, the CA genotype of rs7318578 significantly decreased the risk of liver cancer (OR = 0.61, 95% CI: 0.45–0.83, \( P = 0.001 \), compared with those with the AA genotype. Our findings indicated that MIR17HG polymorphism (rs7318578) contributes to liver cancer susceptibility to the Chinese Han population. Further studies with larger samples are required to confirm the results, as well as functional studies to determine the role of this SNP in miRNA expression or molecular pathways.

**Introduction**

Liver cancer is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018, with about 841,000 new cases and 782,000 deaths annually [1]. Liver cancer is also commonly diagnosed and identified as leading causes of cancer death in China, with an estimated about 392,868 newly liver cancer cases and 368,960 death in 2018 [2]. The carcinogenesis of liver cancer is a complex and multistep process regulated by various risk factors. Epidemiological studies indicated that the major environmental risk factors of liver cancer include chronic infections of hepatitis B virus (HBV) and hepatitis C virus, exposure to aflatoxin, alcohol consumption and cigarette smoking, and diabetes [3,4]. Although many individuals are exposed to these risk factors, only a small group of exposed people eventually develop liver cancer, suggesting that host genetic factors may affect liver cancer development. Recently, numerous evidences have revealed that single-nucleotide polymorphisms (SNPs) are associated with liver cancer risk [5–8].

MicroRNAs (miRNAs) are small noncoding single-stranded RNA molecules of about 22 nucleotides, which can regulate target gene expression through complementary binding to their 3’ untranslated region with their seed sequences [9]. MiRNAs have been found to regulate various functions during cancer development, including cancer cell growth, metastasis, cell cycle, apoptosis, invasion, and chemo-resistance...
The human miRNA 17-92 cluster host gene (MIR17HG) located on chromosome 13q31.3 in the third intron of the c13orf25 (chromosome 13 open reading frame 25) gene, encompasses six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a-1) over ∼800 nucleotides. These miRNAs were previously identified to be highly expressed in various types of human cancers, such as lung cancer [12], breast cancer [13], colon cancer [14], pancreatic cancer [15] and gastric cancer [16]. It has demonstrated that miR-92a highly expressed in hepatocellular carcinoma (HCC). In addition, the proliferation of HCC-derived cell lines was enhanced by miR-92a and inhibited by the anti-miR-92a antagonir [17]. A systematic evaluation of candidate oncomiRs and found that up-regulation of miR-18a in HCC was associated with poor patient survival and promoted proliferation in HCC cell lines [18]. However, it remains unclear the mechanism by which miR-17-92 cluster is involved in hepatocellular carcinogenesis.

It has been reported that the MIR17HG polymorphisms were associated with the risk of breast cancer [19], colorectal cancer [20,21] and multiple myeloma [22]. However, the association of the SNPs (rs75267932, rs72640334, rs7318578 and rs17735387) in MIR17HG with liver cancer susceptibility has not been investigated. Therefore, we performed a case–control (432 liver cancer patients and 430 healthy controls) study to assess whether these four genetic variants are associated with the risk of liver cancer in the Chinese Han population.

Materials and methods

Participants
The present study recruited 862 unrelated subjects that visited the Second Affiliated Hospital of Shaanxi University of Chinese Medicine, including 432 patients with liver cancer and 430 healthy control individuals. All the patients with liver cancer were diagnosed by either histopathologic or imaging evidence based on the standards established by the Chinese Society of Liver Cancer (CSLC). The controls are selected from undergoing routine medical examination, which has been excluded those with medical history of surgery, cancer and other diseases. All subjects were unrelated Chinese Han nationality.

DNA extraction
Genomic DNA was extracted from stored blood using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi’an, China) depending on the manufacturer’s instructions [23,24]. The concentration and purity of extracted DNA determined using a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, U.S.A.).

Genotyping
We selected four SNPs (rs75267932, rs72640334, rs7318578 and rs17735387) in MIR17HG with a minor allele frequency (MAF) >5% in the global population from the HapMap database. The primers for polymerase chain reaction (PCR) amplification and single base extension of the three SNPs were designed by the Agena Bioscience Assay Design Suite V2.0 software (https://agenacx.com/online-tools/). The four SNPs genotyping were performed using the Agena MassARRAY platform with iPLEX gold chemistry (Agena Bioscience, San Diego, CA, U.S.A.) according to the manufacturer’s instructions. Data were managed and analyzed using the version 4.0 Agena Bioscience TYPER software.

Statistical analysis
We used the SPSS 20.0 statistical package (SPSS, Chicago, IL) to conduct the basic descriptive statistical analysis of demographic. The chi-squared (χ²) test was used to assess the differences in distribution of gender between the case and control groups. The Student’s t-test analysis was used to compare the distribution of age between liver cancer patients and controls. The Chi-square analysis was also used to confirm that the genotype distribution of each SNP among the control group was in Hardy–Weinberg equilibrium (HWE). The association for polymorphisms in MIR17HG and the liver cancer was assessed under the genetic models (codominant, dominant, recessive and additive) by PLINK software (version 1.07). The genotype and allele frequencies of the four SNPs were compared between liver cancer patients and control subjects with the chi-square test, and the odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression analysis. All statistical analyses were two sided and P-value of less than 0.05 was considered statistically significant.

Results
Table 1 shows the statistical analysis of the demographic characteristics of study participants. There were 432 patients
Table 1 Characteristics of liver cancer patients and controls in the present study

| Characteristics | Cases (%) | Controls (%) | P  |
|-----------------|-----------|--------------|----|
| Total           | 432       | 430          |    |
| Gender          |           |              |    |
| Male            | 344 (79.6)| 342 (79.5)   | 0.846|
| Female          | 88 (20.4) | 88 (20.5)    |    |
| Age (year)      |           |              |    |
| Mean ± SD       | 55.09 ± 11.59 | 55.22 ± 10.73 | 0.861|
| BMI             |           |              |    |
| Mean ± SD       | 24.52 ± 4.52  | 24.36 ± 4.29  | 0.571|
| Smoking         |           |              |    |
| Yes             | 183 (42.4)| 173 (40.2)   | 0.556|
| No              | 249 (57.6)| 257 (59.8)   |    |
| Drinking        |           |              |    |
| Yes             | 168 (38.9)| 162 (37.7)   | 0.714|
| No              | 264 (61.1)| 268 (62.3)   |    |
| Tumor history   |           |              |    |
| Yes             | 50 (11.6) | 18 (4.2)     | <0.001|
| No              | 382 (88.4)| 412 (95.8)   |    |
| Tumor stage     |           |              |    |
| I-II            | 274 (63.0)|            |    |
| III-IV          | 161 (37.0)|            |    |

P<0.05 indicates statistical significance.

Table 2 Allele frequencies distribution and association with liver cancer risk

| SNP–ID          | Chr, Position | Role | Allele A/B | MAF  | HWE–P | OR (95%CI) | P      |
|-----------------|---------------|------|------------|------|-------|------------|--------|
| rs75267932      | 13, 91351812  | Intron | G/A       | 0.116 | 0.461 | 1.04 (0.78–1.41) | 0.775 |
| rs72640334      | 13, 91352674  | Intron | A/C       | 0.115 | 0.560 | 1.34 (0.98–1.83) | 0.069 |
| rs7318578       | 13, 9135215   | Intron | C/A       | 0.377 | 0.727 | 1.45 (1.18–1.77) | 3.04E-04 |
| rs17735387      | 13, 91353800  | Intron | A/G       | 0.201 | 0.652 | 1.00 (0.79–1.27) | 0.971 |

Abbreviations: CI, confidence interval; Chr, chromosome; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

P<0.05 indicates statistical significance.

P<(0.05/4 = 0.0125) indicates statistical significance with Bonferroni correction.

with liver cancer (344 males and 88 females) and 430 healthy controls (342 males and 88 females) in the present study. The average ages of cases and controls were 55.09 years old and 55.22 years old, respectively. No significant differences existed between the case group and the control group in regard to gender, smoking, and drinking (P>0.05). Similarly, no significant differences were found in terms of mean age (P=0.861) and BMI (P=0.571) between these two groups.

Four selected SNPs in MIR17HG were successfully genotyped (call rate >95%). Allele distributions and associations of the MIR17HG gene polymorphisms with liver cancer risk are shown in Table 2. The genotypes of rs75267932, rs72640334, rs7318578 and rs17735387 were in agreement with the HWE in control group (P>0.05). In the overall analysis, we found that the allele C of rs7318578 with the higher distribution frequency in the controls than cases (0.377 vs. 0.294, P=3.04E-04). The SNP rs7318578 was associated with higher risk of liver cancer with an OR 1.45 (95% CI: 1.18–1.77). The association remained significant even after Bonferroni correction, the significant level is 0.05/4 = 0.0125. However, no significant association was observed between the three SNPs in MIR17HG (rs75267932, rs72640334 and rs17735387) and liver cancer risk.

To explore the association between the genotype distributions and associations of the four SNPs in MIR17HG with liver cancer risk, we performed four genetic models (codominant, dominant, recessive and additive) analysis before and after adjusted with age and gender, as shown in Table 3. Individuals with the homozygous genotype CC of rs7318578 presented with an increased risk of liver cancer, compared with those with the AA genotype (OR = 3.01, 95% CI: 1.97–4.62, P=4.09E-07; adjusted OR = 3.03, 95% CI: 1.98–4.65, P=3.83E-07). The rs7318578 was also
Table 3 Genetics models analyses of association MIR17HG polymorphisms with liver cancer risk

| SNP-ID   | Model  | Genotype | Case (%) | Control (%) | OR (95% CI) | P    | adjust OR (95% CI) | P    |
|----------|--------|----------|----------|-------------|-------------|------|--------------------|------|
| rs75267932 | Codominant | AA       | 340 (78.7) | 342 (79.4) | 1           |      |                    |      |
|          |        | GA       | 84 (19.4)  | 82 (19.0)  | 1.03 (0.73–1.45) | 0.863 |                |      |
|          |        | GG       | 8 (1.9)    | 7 (1.6)    | 1.15 (0.41–3.21) | 0.790 |                |      |
|          | Dominant | AA       | 340 (78.7) | 342 (79.4) | 1           |      |                    |      |
|          |        | GG-GA    | 92 (21.3)  | 89 (20.6)  | 1.04 (0.75–1.44) | 0.816 |                |      |
|          | Recessive | GA-AA   | 424 (98.1) | 424 (98.4) | 1.14 (0.41–3.18) | 0.798 |                |      |
|          |        | GG       | 8 (1.9)    | 7 (1.6)    | 1           |      |                    |      |
| rs72640334 | Codominant | CC       | 336 (77.8) | 357 (82.8) | 1           |      |                    |      |
|          |        | AC       | 93 (21.5)  | 72 (16.7)  | 1.37 (0.98–1.93) | 0.070 |                |      |
|          |        | AA       | 3 (0.7)    | 2 (0.5)    | 1.59 (0.76–4.60) | 0.611 |                |      |
|          | Dominant | CC       | 336 (77.8) | 357 (82.8) | 1           |      |                    |      |
|          |        | AA-AC    | 96 (22.2)  | 74 (17.2)  | 1.38 (0.98–1.93) | 0.063 |                |      |
|          | Recessive | AC-CC   | 429 (99.3) | 429 (99.5) | 1           |      |                    |      |
|          |        | AA       | 3 (0.7)    | 2 (0.5)    | 1.50 (0.25–9.02) | 0.668 |                |      |
| rs7318578  | Codominant | AA       | 212 (49.3) | 211 (49.3) | 1           |      |                    |      |
|          |        | CA       | 112 (26.0) | 182 (42.5) | 0.61 (0.45–0.83) | 0.002 |                |      |
|          |        | CC       | 106 (24.7) | 35 (8.2)   | 3.01 (1.97–4.62) | 4.09E–07 |        |      |
|          | Dominant | AA       | 212 (49.3) | 211 (49.3) | 1           |      |                    |      |
|          |        | CC-CA    | 219 (50.7) | 217 (50.7) | 1.00 (0.77–1.31) | 0.999 |                |      |
|          | Recessive | CA-AA   | 324 (75.3) | 393 (91.6) | 1           |      |                    |      |
|          |        | CC       | 106 (24.7) | 35 (8.2)   | 3.67 (2.44–5.53) | 4.70E–10 |        |      |
| rs17735387 | Codominant | GG       | 276 (63.9) | 277 (64.3) | 1           |      |                    |      |
|          |        | AG       | 138 (31.9) | 135 (31.3) | 1.03 (0.77–1.37) | 0.863 |                |      |
|          |        | AA       | 18 (4.2)   | 19 (4.4)   | 0.96 (0.49–1.85) | 0.882 |                |      |
|          | Dominant | GG       | 276 (63.9) | 277 (64.3) | 1           |      |                    |      |
|          |        | AA-AA    | 156 (36.1) | 154 (35.7) | 1.02 (0.77–1.34) | 0.907 |                |      |
|          | Recessive | AG-GG   | 414 (95.8) | 412 (95.6) | 1           |      |                    |      |
|          |        | AA       | 18 (4.2)   | 19 (4.4)   | 0.94 (0.49–1.82) | 0.861 |                |      |
|          | Additive |        |            |            | 1.00 (0.80–1.27) | 0.972 |                |      |

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.
Adjust OR (95% CI) were calculated by logistic regression analysis with adjustments for age and gender.
P<0.05 indicates statistical significance.
P<0.05/4=0.0125 indicates statistical significance with Bonferroni correction.

found to be associated with an increased with liver cancer risk in the recessive model (OR = 3.67, 95% CI: 2.44–5.53, P=4.70E–10); adjusted OR = 3.69, 95% CI: 2.45–5.56, P=4.52E–10) and the additive model (OR = 1.35, 95% CI: 1.13–1.63, P=0.001; adjusted OR = 1.35, 95% CI: 1.13–1.62, P=0.001). However, the results showed that CA genotype of rs7318578 was associated with a decreased risk of liver cancer, compared with those with the AA genotype (OR = 0.61, 95% CI: 0.45–0.83, P=0.002; adjusted OR = 0.61, 95% CI: 0.45–0.83, P=0.001). The association also remained significant even after Bonferroni correction (0.05/4 = 0.0125). However, no significant association was found between the SNPs (rs75267932, rs72640334 and rs17735387) in MIR17HG and risk of liver cancer.

We further divided the data into subgroups based on age, gender, smoking, drinking and BMI (Table 4). When stratifying by age, we found that the genotype CC of rs7318578 was significantly associated with an increased risk of liver cancer, compared with the AA genotype and CA-AA genotype in age >55 years old (OR = 3.37, 95% CI: 1.74–6.51, P<0.0001; OR = 3.91, 95% CI: 2.07–7.38, P<0.0001); age ≤55 years old (OR = 2.73, 95% CI: 1.55–4.83, P=0.001; OR = 3.43, 95% CI: 1.99–5.92, P<0.0001); males (OR = 2.77, 95% CI: 1.72–4.46, P<0.0001; OR = 3.44, 95% CI: 2.18–5.42, P<0.0001); females (OR = 4.30, 95% CI: 1.60–11.60, P=0.004; OR = 4.93, 95% CI: 1.89–12.84, P=0.001); no smoking (OR = 3.46, 95% CI: 1.90–6.30, P<0.0001; OR = 4.13, 95% CI: 2.32–7.33, P<0.0001); smoking (OR = 2.72, 95% CI: 1.46–5.07, P<0.0001; OR = 3.43, 95% CI: 1.89–6.23, P<0.0001); no drinking (OR = 2.96, 95% CI: 1.70–5.17, P<0.0001; OR = 3.72, 95% CI: 2.17–6.37, P<0.0001); drinking (OR = 3.30, 95% CI: 1.67–6.52,
Table 4 Association of rs7318578 with liver cancer risk

| Model     | Genotype | Case (%) | Control (%) | OR (95% CI) | P(case) | control | OR (95% CI) | P       |
|-----------|----------|----------|-------------|-------------|---------|----------|-------------|---------|
| Age       |          | >55      |             |             |         |          |             |         |
| Codominant| AA       | 101 (48.6) | 94 (50.8) | 1           | 111 (50) | 117 (48.1) | 1           |         |
|           | CA       | 57 (27.4) | 77 (41.6) | 0.68 (0.44–1.07) | 0.094 | 55 (24.8) | 105 (43.2) | 0.56 (0.37–0.86) | 0.007 |
|           | CC       | 50 (24) | 14 (7.6) | 3.37 (1.74–6.51) | <0.0001 | 56 (25.2) | 21 (8.6) | 2.73 (1.55–4.83) | 0.001 |
| Dominant  | AA       | 101 (48.6) | 94 (50.8) | 1           | 111 (50) | 117 (48.1) | 1           |         |
|           | CC-CA    | 107 (51.4) | 91 (49.2) | 1.09 (0.74–1.63) | 0.658 | 111 (50) | 126 (51.9) | 0.93 (0.64–1.34) | 0.698 |
|           | CA-AA    | 158 (76) | 171 (92.4) | 1           |         | 166 (74.8) | 222 (91.4) | 1           |         |
| Recessive | CA       | 50 (24) | 14 (7.6) | 3.91 (2.07–7.38) | <0.0001 | 56 (25.2) | 21 (8.6) | 3.43 (1.99–6.92) | <0.0001 |
| Additive  |          | 1.41 (1.08–1.86) | 0.013 |          |         | 1.29 (1.01–1.66) | 0.043 |         |
| Gender    | Male     | 170 (49.6) | 163 (48.1) | 1           |         | 111 (50) | 117 (48.1) | 1           |         |
|           | Female   | 163 (48.4) | 163 (48.1) | 1           |         | 104 (48.3) | 117 (48.1) | 1           |         |
|           |          | 1.42 (1.08–1.86) | 0.013 |          |         | 1.30 (1.01–1.66) | 0.030 |         |
| Smoking   | No       | 118 (48) | 124 (48.6) | 1           |         | 93 (50.8) | 86 (50) | 1           | <0.0001 |
|           | Yes      | 56 (22.8) | 100 (47.4) | 0.50 (0.32–0.81) | 0.045 | 50 (23.8) | 83 (38.4) | 0.74 (0.48–1.14) | 0.15   |
|           |          | 2.91 (1.60–5.27) | 0.001 |          |         | 1.60 (1.00–2.57) | 0.051 |         |
| Drinking  | No       | 139 (53) | 135 (50.9) | 1           | <0.0001 | 73 (43.5) | 75 (46.3) | 1           | <0.0001 |
|           | Yes      | 62 (23.7) | 110 (41.5) | 0.66 (0.45–0.98) | 0.029 | 50 (23.8) | 83 (38.4) | 0.70 (0.43–1.14) | 0.15   |
|           |          | 2.91 (1.60–5.27) | 0.001 |          |         | 1.60 (1.00–2.57) | 0.051 |         |
| BMI       | <24      | 108 (49.1) | 96 (45.5) | 1           | <0.0001 | 104 (49.5) | 114 (52.8) | 1           | <0.0001 |
|           |          | 0.50 (0.32–0.76) | 0.029 |          |         | 0.74 (0.48–1.14) | 0.15   |         |
|           |          | 2.88 (1.60–5.27) | 0.001 |          |         | 1.60 (1.00–2.57) | 0.051 |         |

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

OR (95% CI) were calculated by logistic regression analysis with adjustments for age and gender. 
P<0.05 indicates statistical significance.
P<0.05/4 = 0.0125 indicates statistical significance with Bonferroni correction.

P<0.0001; OR = 3.87, 95% CI: 2.03–7.38, P<0.0001; BMI > 24 (OR = 3.32, 95% CI: 1.76–6.25, P<0.0001; OR = 4.46, 95% CI: 2.43–8.18, P<0.0001; BMI ≤ 24 (OR = 2.88, 95% CI: 1.60–5.21, P<0.0001; OR = 3.24, 95% CI: 1.84–5.72, P<0.0001).
In the additive model, rs7318578 was found to be associated with significantly increased risk of liver cancer in the age >55 years old (OR = 1.41, 95% CI: 1.08–1.86, \(P=0.013\)), age ≤55 years old (OR = 1.29, 95% CI: 1.01–1.66, \(P=0.043\)); males (OR = 1.30, 95% CI: 1.06–1.59, \(P=0.013\)), females (OR = 1.57, 95% CI: 1.05–2.37, \(P=0.030\)); no smoking (OR = 1.39, 95% CI: 1.08–1.78, \(P=0.009\)), smoking (OR = 1.33, 95% CI: 1.01–1.74, \(P=0.042\)); no drinking (OR = 1.29, 95% CI: 1.02–1.63, \(P=0.033\)), drinking (OR = 1.47, 95% CI: 1.09–1.97, \(P=0.010\)); BMI > 24 (OR = 1.32, 95% CI: 1.01–1.70, \(P=0.037\)), BMI ≤ 24 (OR = 1.40, 95% CI: 1.08–1.81, \(P=0.011\)) (Table 4).

However, the CA genotype of rs7318578 significantly decreased the risk of liver cancer in age ≤55 years old (OR = 0.56, 95% CI: 0.37–0.86, \(P=0.007\)); males (OR = 0.59, 95% CI: 0.42–0.82, \(P=0.002\)); no smoking (OR = 0.66, 95% CI: 0.45–0.98, \(P<0.0001\)), smoking (OR = 0.54, 95% CI: 0.33–0.87, \(P<0.0001\)); no drinking (OR = 0.55, 95% CI: 0.37–0.81, \(P<0.0001\)); BMI > 24 (OR = 0.50, 95% CI: 0.32–0.76, \(P<0.0001\)), compared with the AA genotype (Table 4).

**Discussion**

In the present study, we investigated the association between MIR17HG polymorphisms and liver cancer risk in the Chinese Han population. Overall, stratification analysis found that the rs7318578 was significantly associated with increased the risk of liver cancer in allele, recessive and additive models. Overall, stratification analysis results indicated that individuals with the homozygous genotype CC of rs7318578 presented with an increased risk of liver cancer; however, the CA genotype of rs7318578 significantly decreased the risk of liver cancer in overall, male and age ≤55 years old, compared with those with the AA genotype.

This MIR17HG gene is the host gene for the MIR17-92 cluster, a group of at least six microRNAs (miRNAs) that may be involved in cell survival, proliferation, differentiation and angiogenesis [25]. The miR-17-92 gene cluster, also known as C13orf25, is closely related to tumorigenesis by inhibiting the expression of cell cycle regulatory genes and tumor suppressor genes. The E2F, p53, STAT3 and c-Myc bind to the promoter region of the miR-17-92 gene cluster and regulate downstream target genes, thereby affecting biological processes such as cell proliferation, invasion, migration and apoptosis, playing an important role in tumorigenesis [26–28]. The oncogenic effect of the miR-17-92 cluster is enhanced by cooperation between its members in targeting tumor-suppressive proteins and pathways such as PTEN and TGFβ signaling [29]. MiR-17-92 cluster is an oncogenic miRNA cluster that is implicated in several cancers. The miR-17-92 cluster has been reported to be highly expressed in human hepatocellular carcinoma (HCC) tissues compared with the non-tumorous liver tissues by reverse transcription-polymerase chain reaction (RT-PCR) and in situ hybridization analyses. Moreover, forced overexpression of the miR-17-92 cluster in cultured human hepatocellular cancer cells enhanced tumor cell proliferation, colony formation and invasiveness in vitro, whereas inhibition of the miR-17-92 cluster reduced tumor cell growth [30]. A recent study shows that the histone deacetylase inhibitors (HDACi) SAHA epigenetically upregulates MICA expression through regulating the expression of miR-17-92 cluster and MCM7 in hepatoma. Thus, enhancing the sensitivity of HCC to natural killer cell-mediated lysis [31]. These findings suggest that miR-17-92 cluster plays a pivotal role in the development of liver cancer. However, its role in hepatocarcinogenesis has not been clearly established.

It has been reported that the rs7336610 and AC haplotype of rs4824505/rs7336610 are associated with risk of breast cancer [19]. Polymorphisms (rs7336610 and rs1428), haplotype AC (rs4284505-rs1428) and CA (rs7336610-rs4284505) of MIR17HG were correlated with increased multiple myeloma risk, whereas haplotype GC (rs4284505-rs1428) significantly elevated multiple myeloma risk [22]. Meanwhile, Kaplan–Meier curve analysis demonstrated that the CC genotype of rs7336610 and the AA genotype carriers of rs4284505 had higher 5-year survival. Previous study reported that two functional polymorphisms (rs9588884 and rs982873) in the promoter region of miR-17-92 cluster are associated with a decreased risk of colorectal cancer [20]. Recently, Chen et al. [21] indicated that the two SNPs (rs7336610 and rs1428) of MIR17HG were associated with increased colorectal cancer risk, and the two SNPs (rs7318578 and rs17735387) of MIR17HG were associated with decreased colorectal cancer risk in the Chinese Han population. In the present study, we investigate the association between polymorphisms of MIR17HG and liver cancer risk in the Chinese Han population. The results indicated that the genotype CC of rs7318578 was associated with an increased risk of liver cancer; however, the CA genotype of rs7318578 significantly reduced the risk of liver cancer, compared with those with the AA genotype. In the genomes project in Han Chinese, the frequency of allele C of rs7318578 is 0.277; the frequencies of genotype AA, AC and CC are 0.515, 0.417 and 0.068, respectively. In the present study control group, the frequency of allele C of rs7318578 is 0.294; the frequencies of genotype AA, AC and CC are 0.493, 0.425 and 0.082, respectively. There was no significant difference in the frequency distribution of alleles \(P=0.616\) and genotypes \(P=0.865\) of rs7318578 between this study control group and genomes project CHB. Therefore, the further research is needed to verify the results.
To the best of our knowledge, the present study is the first to assess the association between polymorphisms in the *MIR17HG* gene and liver cancer risk in the Chinese Han population. The limitations of our work should be mentioned. First, the sample size of the present study is relatively small. Second, limited the gene–environment interaction analysis. Third, additional SNPs in *MIR17HG* may be associated with liver cancer but were not assessed for their potential associations. Finally, the present study did not elucidate the role of this SNP in miRNA expression or the specific mechanism of the *MIR17HG* polymorphisms affecting in the development of liver cancer.

**Conclusions**

In conclusion, our study provides evidence that polymorphism (rs7318578) in *MIR17HG* was associated with susceptibility to liver cancer in the Chinese Han population. To the best of our knowledge, this is the first time study investigating SNPs in the *MIR17HG* gene in liver cancer. Therefore, our findings are required to confirm in further with larger populations and/or different ethnicities, as well as functional studies to determine the role of this SNP in miRNA expression or molecular pathways affecting in the development of liver cancer.

**Data Availability**
The data used to support the findings of this study are available from the corresponding author upon request.

**Competing Interests**
The authors declare that there are no competing interests associated with the manuscript.

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**Author Contribution**
Chao Jiang contributed to the study conception and design. Xu Chao and Xuesong Feng collected and analyzed the data. Hailong Shi and Yuewen Wang performed the experiments. Lanlang Wang and Haiyu Shen contributed to the manuscript writing. Qing Zha and Yanni Chen prepared the reagents/materials. All coauthors provided final approval of the manuscript.

**Ethics Approval**
This study was approved by the Second Affiliated Hospital of Shaanxi University of Chinese Medicine, and was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed written consent for blood samples collection and subsequent analysis at recruitment.

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**Abbreviations**
CI, confidence interval; HCC, human hepatocellular carcinoma; HDACi, histone deacetylase inhibitors; OR, odds ratio; RT-PCR, reverse transcription-polymerase chain reaction; SNP, single-nucleotide polymorphism.

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