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# Associations between polymorphisms of the *ACYP2* gene and Liver cancer risk: A case-control study and meta-analysis

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## Abstract

**Background:** *ACYP2* gene may be involved in the process of telomere shortening which may be involved in the liver cancer. So, this research was to examine whether the *ACYP2* gene polymorphism has impact on the risk of liver cancer in Chinese population.

**Methods:** Two hundred and fifty cirrhosis patients and 248 liver cancer patients were selected. Unconditional logistic regression was to calculate the odds ratio (OR) and 95% confidence intervals (CIs). Analyze the relationship between ACYP2 gene polymorphism and tumor using meta-analysis. Analyze the expression of ACYP2 gene in liver cancer and its influence on the prognosis of liver cancer by databases (Ualcan, GTEX and Kaplan–Meier plotter).

**Results:** In the allele model, *ACYP2* rs843720 was protection against the occurrence of cirrhosis developed into liver cancer (OR = 0.76, 95% CI: 0.58–0.99, $p = 0.04$). Rs1682111 and rs843720 play a protective role in the additive model (rs1682111: OR = 0.69, 95% CI: 0.52–0.93, $p = 0.01$; rs843720: OR = 0.73, 95% CI: 0.54–0.98, $p = 0.04$).While rs843645 G allele increased the risk of cirrhosis developed into liver cancer under the additive model (OR = 1.42, 95% CI: 1.02–2.00, $p = 0.04$). The haplotype analysis detected that "ATATCGCC" decreased the risk of cirrhosis developed into liver cancer (OR = 0.69, 95% CI: 0.51–0.92, 95% CI: $p = 0.013$); however, "TGAGCGTC" increased the risk of cirrhosis developed into liver cancer (OR = 1.48, 95% CI: 1.04–2.10, $p = 0.027$). Meta-analysis shown that *ACYP2* rs1682111 was associated with the risk of cancer (OR = 0.90, 95% CI: 0.78–1.05, $p = 0.02$). ACYP2 gene high expression was found to be associated with better OS for all liver patients.

**Conclusion:** Based on this research, we surmised that *ACYP2* gene may be involved in the occurrence of liver cancer in Chinese populations.

**KEYWORDS**

*ACYP2* gene, case–control study, meta-analysis, liver cancer

*Joint first authors.

# 1 | INTRODUCTION

Primary liver cancer is a kind of cancer that occurs to the liver parenchymal cells or intrahepatic bile duct epithelial cells, which has a high degree of malignancy and short survival (Ferlay et al., 2014). The occurrence of liver cancer is the result of environmental, genetic and living habits, and other factors, is a multi-stage and multi-step process, the pathogenesis is complex, there is interaction between the various factors, including hepatitis B virus infection, smoking, drinking, and exposure to environmental carcinogens is a risk factor (Gao et al., 2012). With the increase in the risk of smoking, the incidence of liver cancer will increase. Alcohol consumption is another factor that cannot be ignored in the occurrence of liver cancer. To some extent, excessive drinking can lead to alcoholic fatty liver cirrhosis and thus increase the incidence of liver cancer. In addition, cirrhosis has been recognized that the most important clinical risk factor for the development of liver cancer (Nordenstedt, White, & El-Serag, 2010).

Human telomeres complexes are composed of repetitive nucleotide sequences (TTAGGG) and nucleoproteins, which protect chromosome ends of end-to-end fusions and degradation to maintain genomic integrity (Shay & Wright, 2011). A number of studies show that from the normal liver tissue, chronic hepatitis, cirrhosis of the liver tissue, large regenerative nodule, and dysplastic nodules to liver cancer tissues, the telomere length shorten, prompt telomere shortening may be involved in the occurrence of liver cancer (Isokawa et al., 1999; Plentz et al., 2004). Codd et al. found that *ACYP2* rs11125529 was associated with mean LTL ($p < 5 \times 10^{-8}$) (Codd et al., 2013). Therefore, we speculate that ACYP2 gene affects the development of liver cancer by affecting telomere length. Therefore, the mutation of *ACYP2* may be involved in the occurrence of tumorigenesis (Calamai et al., 2005). So far, discusses on the relationship between the *ACYP2* gene and liver cancer is still less. So, the purpose of this research was to examine whether the *ACYP2* gene polymorphism has impact on the risk of liver cancer in Chinese population. In this research, we selected 13 loci in *ACYP2* gene to research the influence on the risk of cirrhosis developed into liver cancer, which rs11125529 in *ACYP2* gene was reported to be associated with telomere length, other sites were selected according to the minimum allele frequency more than 0.05 in the HapMap Chinese Han Beijing population.

# 2 | MATERIALS AND METHODS

## 2.1 | Ethics statement

This study strictly followed the principles of the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee of Haikou people's Hospital and Peking University Shenzhen Hospital. We confirmed that all research was performed in accordance with relevant regulations. Informed consent forms were signed by all participants. We confirmed that informed consent was obtained from all participants and their legal guardians.

## 2.2 | Study population

From March 2015 to November, 2016, a total of 498 patients were selected, including 250 patients with cirrhosis as control group, and 248 patients with liver cancer as case group. The samples of liver cancer were developed from cirrhosis. The diagnostic criteria of patients based on the American Association for the Study of Liver Disease. Liver cirrhosis was diagnosed either by histopathologically diagnosis, ultrasound, computer tomography (CT), or magnetic resonance imaging (MRI). The liver cancer were diagnosed based on pathological identification combined with at least one positive liver image on computed tomography, magnetic resonance imaging, or ultrasonography, occasionally combined with increased serum AFP levels (>400 ng/ml). Patients who had organ transplantation were excluded from this study.

## 2.3 | SNP Genotyping

In this research, we selected 13 loci in *ACYP2* gene to research the influence on the risk of cirrhosis developed into liver cancer, which rs11125529 in *ACYP2* gene was reported to be associated with telomere length (Codd et al., 2013), other sites were selected according to the minimum allele frequency more than 0.05 in the HapMap Chinese Han Beijing population. DNA extraction was performed using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd. Xi'an City, China), and the DNA concentration was measured using Nanodrop 2000(Gene Company Limited); the primers, which used in genotyping, were designed by the Agena MassARRAY Assay Design 3.0 Software (Gabriel, Ziaugra, & Tabbaa, 2009). Agena MassARRAY RS1000 was used for genotyping, and the related data were managed using Agena Typer 4.0 Software (Gabriel et al., 2009; Thomas et al., 2007).

## 2.4 | Statistical analysis

Data analysis was performed using Microsoft Excel (Redmond, WA) and SPSS 19.0 statistical package (SPSS, Chicago, IL). All $p$ values were two-sided, and $p < 0.05$ was indicated statistical significance. Bonferroni's adjustment for multiple tests was applied to the level of significance for allele model, which was set at $P$ less than 0.05/(13*1). Bonferroni's adjustment for multiple tests was applied to the level of significance for three genetic models analysis, which was set at $p$ less than 0.05/(13*3). Each SNP frequency in the control subjects was assessed for departure

from Hardy–Weinberg Equilibrium (HWE) using an exact test. We calculated genotype frequencies of cases and controls using a $\chi^2$ test (Adamec, 1964). Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using unconditional logistic regression with adjustment for age and sex (Bland & Altman, 2000). We used the power and sample size (PS) Calculation software (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) to calculate the power of the significant difference (Dupont & Plummer, 1998).

Three genetic models (dominant, recessive, and additive model) were performed using PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/), to characterize the potential association of each polymorphism with the risk of cirrhosis developed into liver cancer. We used Haploview software package (version 4.2) to do haplotype analysis used 250 control samples. First, we make linkage disequilibrium analysis. Using the parameter D' and $r^2$ to measure the degree of linkage disequilibrium between the two SNPs loci. Using D' confidence interval method divided haplotype block haplotype block. $|D'| \leq 1$, the more close to 1, the higher the level of linkage disequilibrium between sites; $R^2 \leq 1$, the more close to 1, the higher the level of linkage disequilibrium between the loci. The odds ratios (ORs) and 95% confidence intervals (CIs) of haplotype were determined using unconditional logistic regression with adjustment for age and sex (Barrett, Fry, Maller, & Daly, 2005; Hawley & Kidd, 1995).

## 2.5 | Meta-analysis

We conducted searches of PubMed, EMBASE, and the China National Knowledge Infrastructure (CNKI) using the following search terms: "*ACYP2*", "rs843720", "rs1682111", "rs843645". The search was completed in July of 2018. The articles selected for the subsequent meta-analysis were all published in English in the primary literature, focused on humans, and free of obvious overlap with the subjects of other studies. For rs843720, rs1682111, and rs843645, we found six articles, six articles, and four articles, respectively (Table S1). All statistical analyses were performed using the STATA software (version 11.0; Stata Corporation, College Station, Texas). Two-sided $p$ values less than 0.05 were considered statistically significant. The OR and 95% CI in each case–control study were employed to assess the strength of the associations between *ACYP2* polymorphisms and cancer risk. The OR and 95% CI in each comparison were assessed in the allele model. The $I^2$ statistic was then used to quantitatively estimate heterogeneity, with $I^2$ less than 25%, between 25% and 75%, and greater than 75% representing low, moderate, and high degrees of inconsistency, respectively (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). The significance of the combined OR was determined using a $Z$ test ($p < 0.05$ was considered statistically significant).

## 2.6 | The expression and Kaplan–Meier plotter

We used the UALCAN database to analysis the expression of *ACYP2* gene in HILC and normal tissues (Chandrashekar et al., 2017), and analysis of the effects of gene polymorphism on gene expression via the GTEX database (https://gtexportal.org/). And the patient samples were divided into two cohorts according to the median expression of the ACYP2 gene (high vs. low expression), using Kaplan–Meier plotter and Log rank test to analysis the prognostic significance of mRNA expression of *ACYP2* gene in liver cancer (http://kmplot.com/analysis/).

# 3 | RESULTS

Table 1 shows the basic information of our selected samples, including sample size and age. A total of 498 patients with cirrhosis were selected, which consisted of 248 patients (192 males and 56 females) with cirrhosis developed into liver cancer and 250 cirrhosis patients (124 males and 60 females) without liver cancer. The mean age of liver cancer patients and cirrhosis patients without liver cancer is 54.47 ± 12.05 years and 51.10 ± 10.80 years, respectively. The mean age was statistically different between the case group and the control group, $p = 0.003$.

Table 2 shows the basic information of our selected 13 SNPs, consists of chromosomal, HWE $p$ value, minor allele frequency of all the SNPs. Exact test shown that all the loci were meet the HWE ($p > 0.05$). In the allele model, *ACYP2* rs843720 decreased the risk of cirrhosis developed into liver cancer (OR = 0.76, 95% CI: 0.58–0.99, $p = 0.04$). Finally, after multiple testing corrections, no polymorphisms were found to influence the risk of liver cancer.

We used unconditional logistic regression adjusted for age and sex to calculate the odds ratio (OR) and 95% confidence intervals (CIs) in three genetic models, including dominant model, recessive model, and additive model. We found that *ACYP2* rs1682111 decreased the risk of cirrhosis developed into liver cancer in the additive model (OR = 0.69, 95% CI: 0.52–0.93, $p = 0.01$, power = 0.479) and dominant model (OR = 0.60, 95% CI: 0.41–0.90, $p = 0.01$), respectively. Additive model

**TABLE 1** The sample information of liver cancer and cirrhosis

| | Liver | Cirrhosis | *p* |
|---|---|---|---|
| Gender | 248 | 250 | 0.020 |
| Female | 56 | 60 | |
| Male | 192 | 124 | |
| Mean Age, year | 54.47 ± 12.05 | 51.10 ± 10.80 | 0.003 |

*Note*: $p < 0.05$ indicates statistical significance.

**TABLE 2** Basic information of *ACYP2* gene polymorphism and their associations with cirrhosis developed into liver cancer

| | | | | | | | | Allele model | |
|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **Chromosome** | **Position** | **Band** | **Alleles A/B** | **Gene** | **Role** | **HWE-*p*** | **OR(95% CI)** | ***p*** |
| rs6713088 | 2 | 54345469 | 2p16.2 | G/C | ACYP2 | Intron | 0.62 | 1.25 (0.97–1.61) | 0.09 |
| rs12621038 | 2 | 54391113 | 2p16.2 | T/C | ACYP2 | Intron | 0.41 | 1.21 (0.94–1.56) | 0.13 |
| rs1682111 | 2 | 54427979 | 2p16.2 | A/T | ACYP2 | Intron | 0.6 | 0.78 (0.59–1.01) | 0.06 |
| rs843752 | 2 | 54446587 | 2p16.2 | G/T | ACYP2 | Intron | 0.88 | 1.18 (0.89–1.57) | 0.26 |
| rs10439478 | 2 | 54459450 | 2p16.2 | C/A | ACYP2 | Intron | 0.24 | 1.05 (0.81–1.35) | 0.72 |
| rs843645 | 2 | 54474664 | 2p16.2 | G/T | ACYP2 | Downstream | 0.75 | 1.21 (0.91–1.62) | 0.19 |
| rs11125529 | 2 | 54475866 | 2p16.2 | A/C | ACYP2 | Downstream | 0.41 | 1 (0.73–1.38) | 0.99 |
| rs12615793 | 2 | 54475914 | 2p16.2 | A/G | ACYP2 | Downstream | 0.25 | 1.06 (0.78–1.44) | 0.71 |
| rs843711 | 2 | 54479117 | 2p16.2 | T/C | ACYP2 | Downstream | 0.29 | 1.06 (0.83–1.37) | 0.62 |
| rs11896604 | 2 | 54479199 | 2p16.2 | G/C | ACYP2 | Downstream | 1 | 0.9 (0.67–1.23) | 0.52 |
| rs843706 | 2 | 54480369 | 2p16.2 | A/C | ACYP2 | 3' UTR | 0.34 | 1.06 (0.82–1.36) | 0.66 |
| rs17045754 | 2 | 54496757 | 2p16.2 | C/G | ACYP2 | Intron | 0.55 | 1.07 (0.78–1.46) | 0.69 |
| rs843720 | 2 | 54510660 | 2p16.2 | G/T | ACYP2 | Intron | 0.45 | 0.76 (0.58–0.99) | 0.04 |

*Note*: $p < 0.004$ means that $p < 0.05/13$ indicates statistical significance for multiple comparisons.
Abbreviations: ORs: odds ratios; CI: confidence interval; $p < 0.05$ indicates statistical significance.

**TABLE 3** The relationship between *ACYP2* gene polymorphism and cirrhosis developed into liver cancer adjusted by age and gender

| | | | **Additive model** | | **Dominant model** | | **Recessive model** | | |
|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **Alleles A/B** | **Gene(s)** | **OR(95% CI)** | ***p*** | **OR(95% CI)** | ***p*** | **OR(95% CI)** | ***p*** | **Power** |
| rs1682111 | A/T | ACYP2 | 0.69 (0.52–0.93) | 0.01 | 0.6 (0.41–0.9) | 0.01 | 0.66 (0.36–1.22) | 0.18 | 0.479 |
| rs843645 | G/T | ACYP2 | 1.42 (1.02–2) | 0.04 | 1.5 (1.01–2.23) | 0.05 | 1.67 (0.66–4.24) | 0.28 | 0.400 |
| rs843720 | G/T | ACYP2 | 0.73 (0.54–0.98) | 0.04 | 0.74 (0.49–1.1) | 0.13 | 0.53 (0.28–0.97) | 0.04 | 0.381 |

*Note*: $p < 0.05$ indicates statistical significance.
$p < 0.006$ means that $p < 0.05/(13*3)$ indicates statistical significance for multiple comparisons.
Abbreviations: ORs: odds ratios; CI: confidence interval.

and recessive model indicated that *ACYP2* rs843720 decreased the risk of cirrhosis developed into liver cancer (power = 0.381; additive model: OR = 0.73, 95% CI: 0.54–0.98, $p = 0.04$; recessive model: OR = 0.53, 95% CI: 0.28–0.97, $p = 0.04$). Besides that, additive model revealed that *ACYP2* rs843645 G allele increased the risk of cirrhosis developed into liver cancer (OR = 1.42, 95% CI: 1.02–2.00, $p = 0.04$, power = 0.400; Table 3). Finally, after multiple testing corrections, no polymorphisms were found to influence the risk of liver cancer.

Using the parameters D', $r^2$ to measure the degree of linkage disequilibrium between SNP loci, the D' confidence interval method was used to divide the haplotype block. Figure 1 shown that rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, rs11896604 exist strong linkage. Further haplotype analysis detected that "ATATCGCC" decreased the risk of cirrhosis developed into liver cancer (OR = 0.69, 95% CI: 0.51–0.92, $p = 0.013$; Table 4). While the haplotype "TGAGCGTC" increased the risk of cirrhosis developed into liver cancer (OR = 1.48, 95% CI: 1.04–2.10, $p = 0.027$; Table 4).

In the meta-analysis, we found a significant association between *ACYP2* rs1682111 polymorphisms decreased the risk of cancer in the allele model (OR = 0.90, 95% CI = 0.78–1.05, $p = 0.02$). The forest plots for rs1682111 in the allele model are shown in Figure 2. No correlation between rs843720, rs843645, and tumors was found (Figure S1 and S2).

By UALCAN database, we found that there were differences in the expression of *ACYP2* gene in different tumor stages. The *ACYP2* gene low expression in LIHC grade 3, when compared with the normal tissue (Figure 3), and rs1682111 mutation affects the expression of *ACYP2* gene in the Colon-Sigmoid tissue ($p = 0.000025$) (Figure 4). The expression of the TT genotype was significantly lower than that of the AA genotype. Survival curve revealed that patients with high expression have higher survival rates than patients with low expression. *ACYP2* gene high expression was found

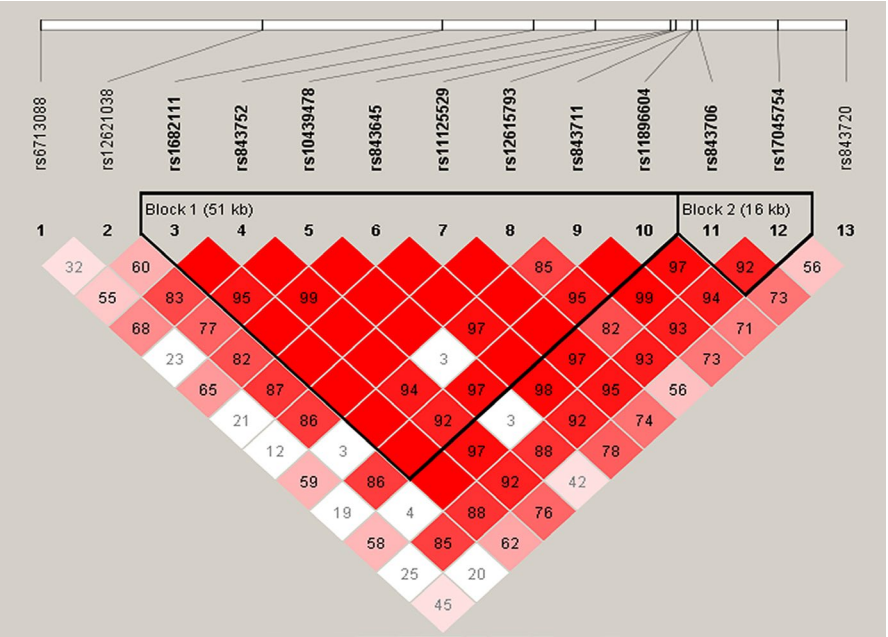


**FIGURE 1** Haplotype block map for all the SNPs of the *ACYP2* gene

**TABLE 4** The haplotype frequencies of *ACYP2* gene polymorphisms and cirrhosis developed into liver cancer risk

| Gene | SNPs | Haplotype | Crude analysis | |
|---|---|---|---|---|
| | | | OR(95% CI) | *p* |
| ACYP2 | rs1682111\|rs843752\|rs10439478\|rs843645\|rs11125529\|rs12615793\|rs843711\|rs11896604 | ATATCGCC | 0.69 (0.51–0.92) | 0.013 |
| | | TTCTCGCC | 1.10 (0.77–1.57) | 0.609 |
| | | TTCTAATG | 1.02 (0.71–1.46) | 0.93 |
| | | TTCTCACC | 1.32 (0.46–3.77) | 0.61 |
| | | TGAGCGTC | 1.48 (1.04–2.10) | 0.027 |
| | | TTCTCGTG | 0.55 (0.15–2.03) | 0.37 |

*Note*: $p < 0.05$ indicates statistical significance.
Abbreviations: ORs: odds ratios; CI: confidence interval.

to be associated with better OS for all liver patients (HR, 0.54; 95% CI, 0.38–0.77; $p = 0.00049$) (Figure 5).

## 4 | DISCUSSION

Liver cancer is a highly inherited malignant tumor with high incidence, concealment, high malignancy, rapid progress, and poor prognosis. Through the case–control study, we found that *ACYP2* rs1682111 and rs843720 were protective factors for cirrhosis developed into liver cancer, while *ACYP2* rs843645 increased the risk of cirrhosis developed into liver cancer.

The study found that *ACYP2* is associated with a variety of tumors or diseases, such as lung cancer (Chen et al., 2016), colorectal cancer (Liu et al., 2017), breast cancer (Zhang et al., 2016), stroke (Liang et al., 2017), high altitude pulmonary edema (He et al., 2016). Cui et al researched the influence of telomere related genes on the prognosis of glioma, found that *ACYP2* rs843720 influence the overall survival rate, the overall survival rate of glioma patients with mutated genotype was lower than that of wild-type patients (Cui et al., 2017). Chen et al. recruited 1,156 participants, assessed the relationship between *ACYP2* gene polymorphism and lung cancer, and revealed that rs1682111 (A/T) and rs843720 (G/T) in *ACYP2* gene promoted the risk of lung cancer (Chen et al., 2016). At the same time, for breast cancer, Zhang et al. research the influence of *ACYP2* gene polymorphism on breast cancer by 183 cases and 195 controls, and found that rs1682111 risk allele A boosted the risk of BC risk, as a risk factor for breast cancer occur (Zhang et al., 2016). In the study of colorectal cancer, also found that *ACYP2* gene promoted the occurrence of colorectal cancer, for colorectal cancer, rs843645 is also a risk factor (Liu et al., 2017). In spite of *ACYP2* gene was found to affect the occurrence of disease in a number of items, *ACYP2* gene and liver cancer genetic susceptibility is unclear. By UALCAN database (http://ualcan.path.uab.edu/index.html) (Chandrashekar et al., 2017), we found that there were differences in the expression of *ACYP2* gene in different tumor stages and different populations. But by the OncoLnc database (http://www.oncolnc.org/) (Anaya, 2016), we found that patients with high expression have higher survival rates than patients with low expression, in patients with liver cancer. *ACYP2* gene high expression was found to be associated with better OS for all liver patients (HR, 0.54; 95% CI, 0.38–0.77; $p = 0.00049$).

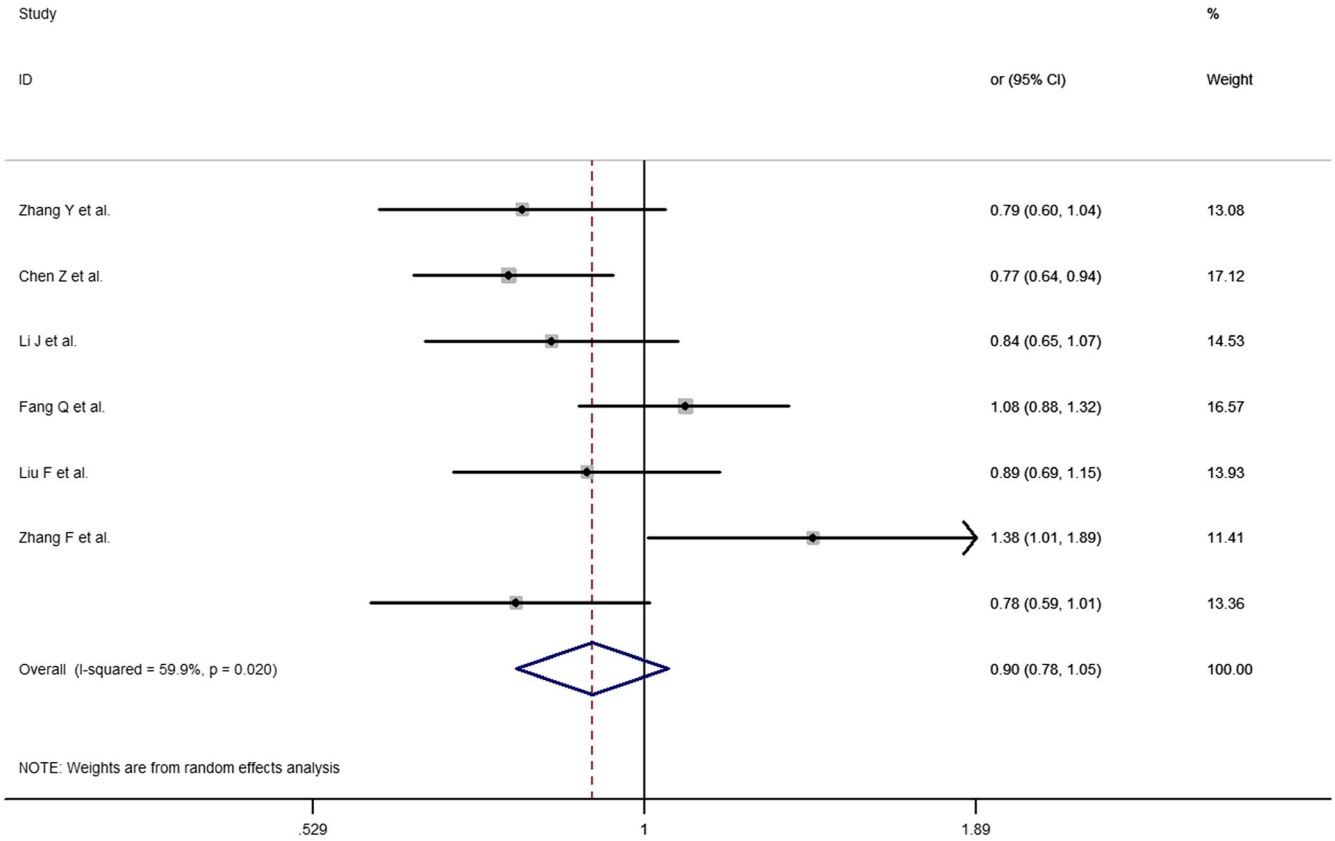


**FIGURE 2** Forest plot of cancer risk associated with the *ACYP2* rs1682111 polymorphism (A vs. T)

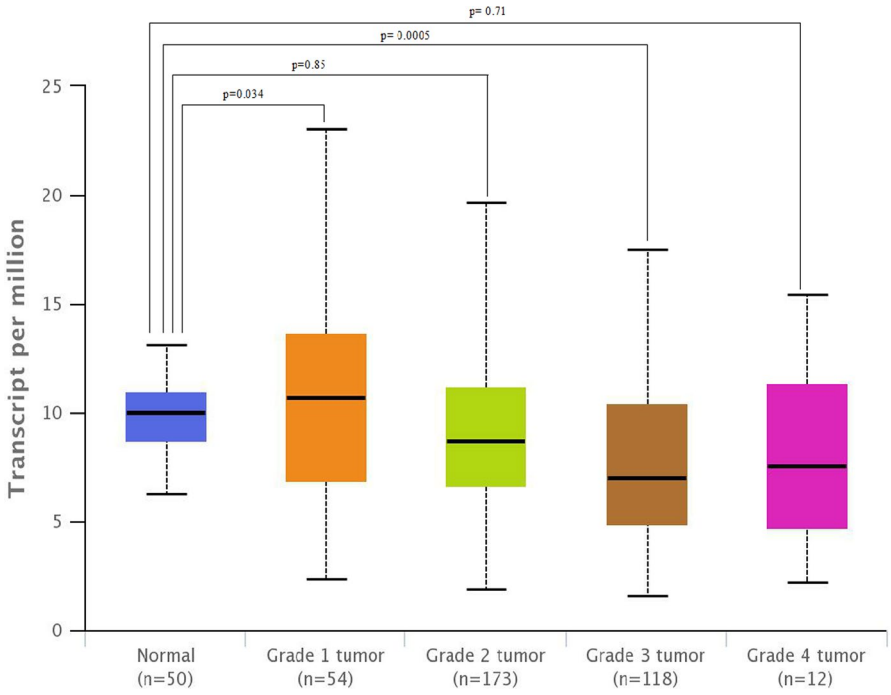


**FIGURE 3** ACYP2 gene expression is down-regulated in LIHC base on tumor grade compared with normal tissues

*ACYP2* gene was related to cell differentiation and apoptosis, and apoptosis or programmed cell death participated in embryonic development, immune system regulation, tissue homeostasis, and prevention of malignant tumors. Therefore, the mutation of *ACYP2* may be involved in the occurrence of tumorigenesis (Calamai et al., 2005). Codd et al. researched

the effects of several genes on telomere length, identifying seven loci, including *ACYP2* rs11125529, which were associated with mean LTL ($p < 5 \times 10^{-8}$) (Codd et al., 2013). From chronic hepatitis, cirrhosis of the liver to the trilogy is the clinical common liver cancer of liver cancer. Previous studies have found that telomere length of the progress of the chronic liver disease gradually shortened, suggesting that in the process of chronic liver disease progression, telomeres shorten involved in the progression of chronic liver disease (Miura et al., 1997). A number of studies show that from the normal liver tissue, chronic hepatitis, cirrhosis of the liver tissue, large regenerative nodule and dysplastic nodules to liver cancer tissues, the telomere length shorten, prompt telomere shortening may be involved in the occurrence of liver cancer (Isokawa et al., 1999; Plentz et al., 2004).

Etiologically, the occurrence of liver cancer related to chronic hepatitis B (HBV) infection, excessive alcohol intake, and metabolic disease. In these samples, only part of the sample has information on smoking and drinking, as a result, we did not analyze the impact of smoking, drinking alcohol on the liver cancer. In a follow-up study, we will try to improve these samples information, explore the genes and the environment (smoking, drinking, etc.) on the interaction of liver cancer.

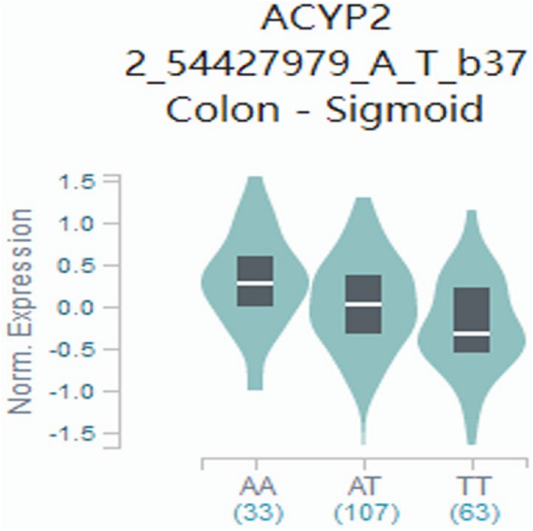


**FIGURE 4** ACYP2 mRNA expression by eQTL analysis in Human Colon—Sigmoid tissue based on GTEx database (rs1682111)

## 5 | CONCLUSIONS

In summary, our study results provided new evidence that *ACYP2* gene was associated with cirrhosis developed into liver cancer in the Chinese Han population and database study provides evidence that *ACYP2* gene was down-regulated in the liver patients, which was harmful to the survival of liver patients. In a follow-up study, selected the liver tissues and control tissues to analysis the expression of *ACYP2* gene in cancer tissues and normal tissues by real-time PCR, and the effects of different genotypes on expression were further analyzed in cancer tissues. Further clarify the role of *ACYP2* gene in the development of liver cancer.

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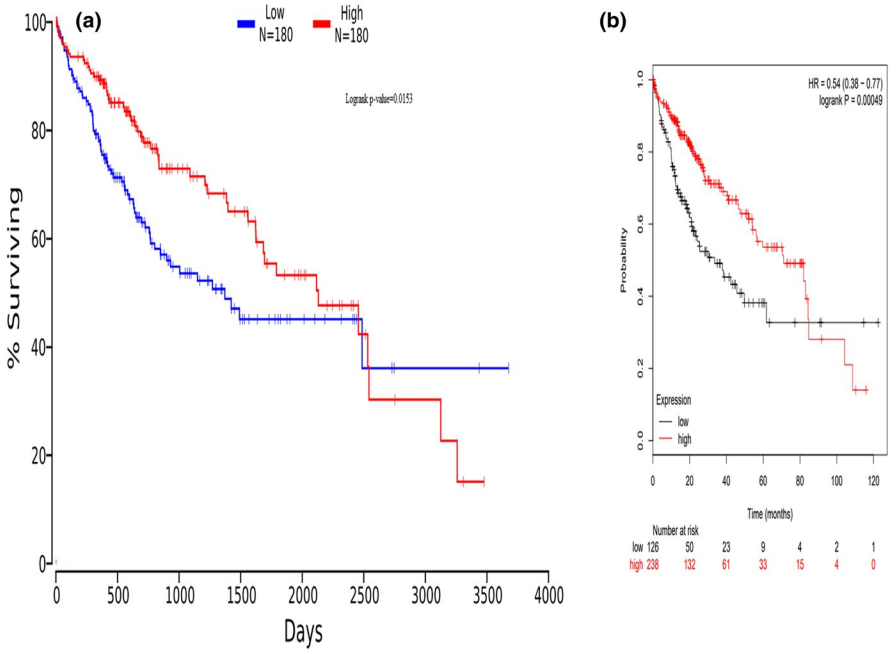
**FIGURE 5** ACYP2 high expression is associated with better survival in liver



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## CONFLICT OF INTEREST

The authors declare that they have no competing interests, and the manuscript is approved by all authors for publication.

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## REFERENCES

Adamec, C. (1964). Example of the use of the nonparametric test. Test X2 for comparison of 2 independent examples. *Cesk Zdrav*, *12*, 613–619.

Anaya, J. (2016). OncoRank: A pan-cancer method of combining survival correlations and its application to mRNAs, miRNAs, and lncRNAs. *PeerJ Preprints*, *4*, e2574v1.

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics*, *21*(2), 263–265. https://doi.org/10.1093/bioinformatics/bth457

Bland, J. M., & Altman, D. G. (2000). Statistics notes. The odds ratio. *BMJ*, *320*(7247), 1468.

Calamai, M., Canale, C., Relini, A., Stefani, M., Chiti, F., & Dobson, C. M. (2005). Reversal of protein aggregation provides evidence for multiple aggregated States. *Journal of Molecular Biology*, *346*(2), 603–616. https://doi.org/10.1016/j.jmb.2004.11.067

Chandrashekar, D. S., Bashel, B., Balasubramanya, S. A. H., Creighton, C. J., Ponce-Rodriguez, I., Chakravarthi, B., & Varambally, S. (2017). UALCAN: A portal for facilitating tumor subgroup gene expression and survival analyses. *Neoplasia*, *19*(8), 649–658. https://doi.org/10.1016/j.neo.2017.05.002

Chen, N., Yang, X., Guo, W., You, J., Wu, Q., Zhang, G., … Zhang, Y. (2016). Association of polymorphisms in the telomere-related gene ACYP2 with lung cancer risk in the Chinese Han population. *Oncotarget*, *7*(52), 87473–87478. https://doi.org/10.18632/oncotarget.13870

Codd, V., Nelson, C. P., Albrecht, E., Mangino, M., Deelen, J., Buxton, J. L., … Samani, N. J. (2013). Identification of seven loci affecting mean telomere length and their association with disease. *Nature Genetics*, *45*(4), 422–427, 427e421-422. https://doi.org/10.1038/ng.2528

Cui, Y., Li, G., Yan, M., Li, J., Jin, T., Li, S., & Mu, S. (2017). The effects of gene polymorphisms on glioma prognosis. *The Journal of Gene Medicine*, *19*(11), 345–352. https://doi.org/10.1002/jgm.2989

Dupont, W. D., & Plummer, W. D. Jr (1998). Power and sample size calculations for studies involving linear regression. *Controlled Clinical Trials*, *19*(6), 589–601.

Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Bray, F. (2014). GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC cancer base no. 11 [Internet]. International Agency for Research on Cancer, Lyon. *International Journal of Cancer Journal International Du Cancer*, *136*(5), E359–E386.

Gabriel, S., Ziaugra, L., & Tabbaa, D. (2009). SNP genotyping using the Sequenom MassARRAY iPLEX platform. *Current Protocols in Human Genetics*, *2*, Unit 2.12. https://doi.org/10.1002/0471142905.hg0212s60

Gao, J., Xie, L., Yang, W. S., Zhang, W., Gao, S., Wang, J., & Xiang, Y. B. (2012). Risk factors of hepatocellular carcinoma–current status and perspectives. *Asian Pacific Journal of Cancer Prevention*, *13*(3), 743–752.

Hawley, M. E., & Kidd, K. K. (1995). HAPLO: A program using the EM algorithm to estimate the frequencies of multi-site haplotypes. *Journal of Heredity*, *86*(5), 409–411.

He, Y., Zhang, X., Li, X., Du, J., He, X., Zhang, Z., … Yuan, D. (2016). Telomere length-related gene ACYP2 polymorphism is associated with the risk of HAPE in Chinese Han population. *The Journal of Gene Medicine*, *18*(9), 244–249. https://doi.org/10.1002/jgm.2896

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558. https://doi.org/10.1002/sim.1186

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Isokawa, O., Suda, T., Aoyagi, Y., Kawai, H., Yokota, T., Takahashi, T., … Abe, Y. (1999). Reduction of telomeric repeats as a possible predictor for development of hepatocellular carcinoma: Convenient evaluation by slot-blot analysis. *Hepatology*, *30*(2), 408–412.

Liang, Y., Zhang, R., Zhang, S., Ji, G., Shi, P., Yang, T., … Chen, M. (2017). Association of ACYP2 and TSPYL6 genetic polymorphisms with risk of ischemic stroke in Han Chinese population. *Molecular Neurobiology*, *54*(8), 5988–5995. https://doi.org/10.1007/s12035-016-0086-x

Liu, F., Zhang, Z., Zhang, Y., Chen, Y., Yang, X., Li, J., & Zhao, J. (2017). Genetic polymorphisms in the telomere length-related gene ACYP2 are associated with the risk of colorectal cancer in a Chinese Han population. *Oncotarget*, *8*(6), 9849–9857. https://doi.org/10.18632/oncotarget.14219

Miura, N., Horikawa, I., Nishimoto, A., Ohmura, H., Ito, H., Hirohashi, S., … Oshimura, M. (1997). Progressive telomere shortening and telomerase reactivation during hepatocellular carcinogenesis. *Cancer Genetics and Cytogenetics*, *93*(1), 56–62.

Nordenstedt, H., White, D. L., & El-Serag, H. B. (2010). The changing pattern of epidemiology in hepatocellular carcinoma. *Digestive and Liver Disease*, *42*(Suppl 3), S206–214. https://doi.org/10.1016/S1590-8658(10)60507-5

Plentz, R. R., Caselitz, M., Bleck, J. S., Gebel, M., Flemming, P., Kubicka, S., … Rudolph, K. L. (2004). Hepatocellular telomere shortening correlates with chromosomal instability and the development of human hepatoma. *Hepatology*, *40*(1), 80–86.

Shay, J. W., & Wright, W. E. (2011). Role of telomeres and telomerase in cancer. *Seminars in Cancer Biology*, *21*(6), 349–353. https://doi.org/10.1016/j.semcancer.2011.10.001

Thomas, R. K., Baker, A. C., Debiasi, R. M., Winckler, W., Laframboise, T., Lin, W. M., … Garraway, L. A. (2007). High-throughput oncogene mutation profiling in human cancer. *Nature Genetics*, *39*(3), 347–351. https://doi.org/10.1038/ng1975

Zhang, F., Zhang, Y., Deng, Z., Xu, P., Zhang, X., Jin, T., & Liu, Q. (2016). Genetic variants in the acylphosphatase 2 gene and the risk of breast cancer in a Han Chinese population. *Oncotarget*, *7*(52), 86704–86712. https://doi.org/10.18632/oncotarget.13495

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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