The influence of ACYP2 polymorphisms on gastrointestinal cancer susceptibility in the Chinese Han population

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Abstract

Background: Gastrointestinal cancer (GI cancer) is a type of cancer that has a high death rate. It has been reported that ACYP2 gene was associated with the development of gastric cancer and colorectal cancer, but it is not clear that the relationship between ACYP2 gene and GI cancer in Chinese Han population. This study aimed to investigate the association between polymorphisms of ACYP2 and GI cancer in the Chinese Han population.

Methods: We used Agena MassARRAY to determine the genotypes of 1,160 GI cancer patients and 495 healthy controls. The correlation between ACYP2 variants and GI cancer risk was examined by logistic regression analysis.

Results: We identified that rs6713088 (OR = 1.17, 95% CI: 1.00–1.36, p = 0.047), rs843711 (OR = 1.17, 95% CI: 1.01–1.36, p = 0.035), and rs11896604 (OR = 1.20, 95% CI: 1.00–1.45, p = 0.048) were correlated with an increased risk of GI cancer under allele model. Rs11125529 under the recessive model (OR = 2.05, 95% CI: 1.00–4.23, p = 0.038), rs843711 in recessive model (OR = 1.37, 95% CI: 1.04–1.82, p = 0.026), and rs11896604 under log-additive model (OR = 1.23, 95% CI: 1.01–1.51, p = 0.042) were associated with an increased risk of GI cancer.

Conclusion: Our study suggested that polymorphisms of ACYP2 gene might be associated with susceptibility to GI cancer.

KEYWORDS
ACYP2 gene, case-control study, gastrointestinal cancer, polymorphisms

1 INTRODUCTION

Gastrointestinal cancer (GI cancer) is a type of tumor that originate in the accessory organs of the digestive tract, including esophageal cancer, gastric cancer, liver cancer, colorectal cancer, and bile duct cancer (Gao, Chen, Xu, Wang, & Yu, 2014). Among the top 10 tumors with the highest mortality rate in the world, GI cancer account for 5 of them, and more than 3 million patients die each year due to GI cancer (Tözün & Vardareli, 2016). The early symptoms of GI cancer are not
obviously, sometimes they are only manifested as wasting, nausea, and abdominal distension (Spiller, 2001). They are easily misdiagnosed with benign diseases such as digestive tract ulcers. Despite the significant improvements in diagnosis and treatment for GI cancer, the 5-year survival rate of the advanced CRC patients is only 8% (Shimada, Tanaka, Endou, & Ichikawa, 2009); 5-year survival rate of GC with metastases is approximately 30% (Yamashita et al., 2011); the 5-year survival rate of liver cancer after surgery is still only 15%-40% (Chen et al., 2016); The overall 5-year survival rate of esophageal cancer is less than 20% (Mariette et al., 2003). Tumor metastasis and lack of effective targeted therapies are the main causes of poor prognosis in patients. However, the pathogenesis of digestive tract tumor is not clear, but a large number of studies have shown that it is caused by the combination of environmental (drinking, smoking, dietary habits, etc.) and genetic factors (ADH1B, ALDH2, SMAD7, PLCE1, PSCA, etc.) (Bass & Meyerson, 2009; Broderick et al., 2007; Heavey & Rowland, 2004; Sakamoto et al., 2008; Wang et al., 2010).

Telomeres are nucleoprotein complexes at the ends of eukaryotic chromosomes (Bonetti, Martina, Falcettoni, & Longhese, 2013). Telomeres maintain chromosome integrity and genomic stability by preventing nucleolytic degradation, chromosomal end-to-end fusion, and irregular recombination (McKnight, Riha, & Shippen, 2002). In general, a critically short telomere length can trigger replicative senescence and cell death (Hiyama & Hiyama, 2007). This can result in genomic instability and chromosomal abnormalities, which can promote carcinogenesis (Duensing & Münker, 2001). It has been reported that telomere-related genes Killer Immunoglobulin-like Receptor (KIR) (Hernandez et al., 2018), protection of telomeres 1 (POT1), telomerase reverse transcriptase (TERT), and telomeric repeat binding factor 2 (TERF2) (Hosgood, Cawthon, He, Chanock, & Lan, 2009) were associated with digestive cancer risk. But the relationship between ACYP2 gene polymorphism and the risk of GI tumors has not been reported.

ACYP2 (Acylphosphatase 2) gene located on chromosome 2p16.2, encodes a small cytosolic acylphosphatase enzyme that catalyzes the hydrolysis of carboxyl-phosphate bonds (Wellmann et al., 2018). Genome wide association study has demonstrated that genetic polymorphisms in ACYP2 are associated with telomere length (He et al., 2016), which has led to studies of the association between ACYP2 and various diseases, including various cancers (Thiesen et al., 2017). A recent paper has indicated a significant association between ACYP2 single nucleotide polymorphisms (SNPs) and testicular cancer (Drögemöller et al., 2018). Thiesen et al. (2017) found that ACYP2 polymorphism was associated with ototoxicity risk in children with cancer. Won et al. (2012) determined that the polymorphism of ACYP2 gene was related to the risk of colorectal cancer. Therefore, we hypothesized that the polymorphism of ACYP2 might be associated with the risk of GI cancer.

There are still few studies on the susceptibility of the ACYP2 gene and the overall GI cancer susceptibility, so the aim of this study was to investigate the impact of several SNPs within ACYP2 gene on GI cancer risk in Chinese Han population.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

All participants were informed both in writing and verbally to the procedures and purpose of the study and signed informed consent documents. The protocols for this study were approved by the Ethical Committee of Shaanxi Provincial People’s Hospital, complied with the World Medical Association Declaration of Helsinki. All the subsequent research analyses were carried out in accordance with the approved guidelines and regulations.

2.2 | Study subjects

A case-control study involving a Chinese study population of 1,160 patients with GI cancer and 495 healthy adults was consecutively enrolled at the Shaanxi Provincial People’s Hospital. All the subjects are genetically unrelated. The GI cancer patients included 386 cases of esophageal cancer, 302 cases of gastric cancer, 247 cases of colorectal cancer, and 225 cases of liver cancer. All the patients were diagnosed by two experienced pathologists, and confirmed, underwent operative treatment for the first time without receiving chemotherapy, radiotherapy, and other treatments. Patients with the following situations were excluded, containing inflammation autoimmune disorders, family history of cancer, and accepted radiotherapy and chemotherapy. Four hundred and ninety-five healthy adults were cancer-free randomly selected from the hospital in the same study period. All of the information of healthy controls interviewed by the professional interviewers, containing age, gender, family history of cancer and occupational exposure to carcinogens, and the person who possessed these unhealthy factors were removed from this study.

2.3 | Data selection

All 11 SNPs had minor allele frequencies >5% according to the global population from the 1,000 Genome Projects (http://www.internationalgenome.org/). Then we used HaploReg (https://pubs.broadinstitute.org/mammals/haploreg/haplo.reg.php) to predict SNP function. Blood samples were collected in ethylene diamine tetraacetic acid (EDTA) tubes and stored at −80°C. Genomic DNA was extracted from 5 ml whole-blood samples using the Whole Blood Genomic DNA Extraction Kit (GoldMag Co. Ltd, Xi’an, Shaanxi, China) following the manufacturer’s protocol. The purity and concentration of the DNA samples were evaluated with the
TABLE 1  Basic characteristics and allele frequencies of the SNPs

| SNP ID   | Gene | Chromosome | Position | Alleles A/B | MAF Case | MAF Control | HWE-p | OR (95% CI) | p     | Function                                      |
|----------|------|------------|----------|-------------|----------|-------------|-------|-------------|-------|-----------------------------------------------|
| rs6713088| ACYP2| 2p16.2     | 54345469 | G/C         | 0.434    | 0.397       | 0.7784 | 1.17 (1.00–1.36) | 0.047 | Selected eQTL hits                           |
| rs12621038| ACYP2| 2p16.2     | 54391113 | T/C         | 0.441    | 0.458       | 0.7862 | 0.93 (0.80–1.08) | 0.365 | Motifs changed, Selected eQTL hits           |
| rs1682111| ACYP2| 2p16.2     | 54427979 | A/T         | 0.297    | 0.303       | 0.8316 | 0.97 (0.83–1.14) | 0.739 | DNAse, Motifs changed, Selected eQTL hits     |
| rs843752  | ACYP2| 2p16.2     | 54,446,587| G/T         | 0.276    | 0.269       | 0.5692 | 1.03 (0.87–1.22) | 0.681 | Motifs changed, Selected eQTL hits           |
| rs10439478| ACYP2| 2p16.2     | 54459450 | C/A         | 0.427    | 0.431       | 0.9271 | 0.98 (0.85–1.14) | 0.852 | Motifs changed, Selected eQTL hits           |
| rs843645  | ACYP2| 2p16.2     | 54474664 | G/T         | 0.263    | 0.261       | 1     | 1.01 (0.85–1.20) | 0.899 | Motifs changed, Selected eQTL hits           |
| rs11125529| ACYP2| 2p16.2     | 54,475,866| A/C         | 0.206    | 0.180       | 0.09185 | 1.18 (0.98–1.43) | 0.081 | Motifs changed, Selected eQTL hits           |
| rs12615793| ACYP2| 2p16.2     | 54475914 | A/G         | 0.221    | 0.191       | 0.04198 | 1.20 (1.00–1.45) | 0.053 | Motifs changed, Selected eQTL hits           |
| rs843711  | ACYP2| 2p16.2     | 54479117 | T/C         | 0.493    | 0.453       | 0.1235 | 1.17 (1.01–1.36) | 0.035 | Motifs changed, Selected eQTL hits           |
| rs1896604  | ACYP2| 2p16.2     | 54479199 | G/C         | 0.225    | 0.194       | 0.2487 | 1.20 (1.00–1.45) | 0.048 | Selected eQTL hits                          |
| rs17045754| ACYP2| 2p16.2     | 54496757 | C/G         | 0.206    | 0.185       | 0.2967 | 1.14 (0.95–1.38) | 0.162 | Selected eQTL hits                          |

Note: *p < 0.01 indicates statistical significance for Hardy–Weinberg equilibrium. *p < 0.05 indicates statistical significance. Bold values indicate a significant difference. Abbreviations: 95% CI, 95% confidence interval; A, minor alleles; B, major alleles; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.
NanoDrop 2000C (Thermo Scientific, Waltham, MA, USA). The isolated DNA was stored at −80°C until analysis.

2.4 SNP genotyping

The genotyping of the 11 SNPs was carried out on the MassARRAY iPLEX (Agena Bioscience, San Diego, CA, USA) platform using the matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) (Lin et al., 2017; Liu, Wang, et al., 2017; Wang et al., 2018). Genotyping results were output by Agena Bioscience TYPER version 4.0 software. Genotyping was carried out by laboratory personnel in a double-blinded fashion. The PCR primers for the SNPs were shown in Table S1.

2.5 Statistical analyses

The student’s t test was applied to assess the differences in the distribution of age between cases and controls, and Pearson’s χ² test was used to evaluate the gender differences in the sample. Genotype frequencies for each SNP were analyzed by Pearson’s χ² test to evaluate departure from Hardy–Weinberg equilibrium (HWE) in control population. Pearson’s χ² test was used to compare the allelic and genotype frequencies of each SNP between patients with GI cancer and controls. Multiple genetic model analyses (codominant, dominant, recessive, and log-additive) were applied using SNPStats (http://bioinfo.iconcologia.net/snpstats/start.htm) software to assess the association between SNPs and GI cancer. Finally, we used Haploview software (version4.2) to construct haplotype and to estimate the pairwise linkage disequilibrium, the SNPStats software platform was used to estimate the correlation between haplotype and GI cancer risk. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression analyses, the wild-type allele was used as a reference (Wang et al., 2015). We performed eQTL analysis to evaluate the effects of different genotypes on ACYP2
gene expression in the digestive tract by GTEx database (Genotype-Tissue Expression, http://www.gtexportal.org/). All \( p \) values of statistical tests were two-sided, and \( p < 0.05 \) was considered as statistically significant.

3 | RESULTS

3.1 | Characteristics of patients and controls

In this case-control study, we collected and analyzed 1,160 cases of GI cancer (846 males and 314 females) and 495 healthy controls (180 males and 315 females). The mean ages of the patients and the controls were \( 58.83 \pm 11.17 \) years and \( 54.48 \pm 9.44 \) years, respectively. The mean age between patients and controls was not matched in present study (\( p < 0.001 \)), and the groups were also not matched by gender (\( p < 0.001 \)).

3.2 | Hardy-Weinberg equilibrium and SNP alleles

The basic information about all the SNPs including gene, band, position, alleles, and functional prediction were presented in Table 1. All SNP genotype distribution in control subjects met the HWE in control group (\( p > 0.05 \)). The differences in the frequency distribution of alleles between cases and controls were compared by Pearson \( \chi^2 \) test. The analyses showed that three variants were observed to associated with GI cancer risk under allele model (rs6713088, \( OR = 1.17, 95\% CI: 1.00–1.36, p = 0.047 \); rs843711, \( OR = 1.17, 95\% CI: 1.01–1.36, p = 0.035 \); rs11896604, \( OR = 1.20, 95\% CI: 1.00–1.45, p = 0.048 \)), and there was no statistical significance found in other eight variants. Furthermore, HaploReg

![FIGURE 1](image-url) Haplotype block map for SNPs of the ACYP2 gene. Linkage disequilibrium plots containing 11 SNPs from ACYP2. Red squares display statistically significant associations between a pair of SNPs, as measured by D'; darker shades of red indicate higher D'.

| Haplotype | Crude OR (95% CI) | p | With adjusted OR (95% CI) | p |
|-----------|------------------|---|----------------------|---|
| rs6713088 | 1.17 (1.00–1.36)  | 0.047 | 1.17 (1.00–1.36) | 0.035 |
| rs843711  | 1.17 (1.01–1.36)  | 0.035 | 1.20 (1.00–1.45) | 0.048 |
| rs11896604| 1.20 (1.00–1.45)  | 0.048 | 1.17 (1.00–1.36) | 0.035 |

Note: \( p < 0.05 \) indicates statistical significance. Abbreviations: CI, confidence interval; OR, odds ratio.
annotation revealed that SNPs associated with GI cancer risk were successfully predicted to have biological functions, and rs6713088, rs843711, and rs11896604 were associated with motifs changed and selected eQTL hits.

### 3.3 Association between ACYP2 polymorphisms and the risk of GI cancer

Genetic models (codominant, dominant, recessive, and log-additive) and the genotype frequencies were used to further identify the associations between the SNPs and the risk of GI cancer (Table 2). The results with adjusted for age and gender showed that the risk of GI cancer would significantly increasing with rs11125529 under the recessive model (adjusted OR = 2.05, 95% CI: 1.00–4.23, \( p = 0.038 \)), rs11896604 under the log-additive model (adjusted OR = 1.23, 95% CI: 1.01–1.51, \( p = 0.042 \)). There were no differences found in genotype frequencies of other SNPs between controls and patients with GI cancer (all \( p > 0.05 \), Table 2).

### 3.4 Association of ACYP2 haplotypes with the risk of GI cancer

Finally, the linkage disequilibrium and haplotype construction were detected and evaluated. One block of ACYP2 SNPs (Figure 1) comprising rs1682111, rs843752, rs843645, and rs843711 comprised rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, and rs11896604 was found in studies by haplotype analysis.

| SNP      | Effect size | \( p \)-value | Tissue                        |
|----------|-------------|---------------|-------------------------------|
| rs6713088| −0.59       | \( 3.10 \times 10^{-30} \) | Esophagus-Mucosa              |
|          | −0.46       | \( 1.10 \times 10^{-17} \) | Colon-Transverse              |
|          | −0.34       | \( 2.60 \times 10^{-14} \) | Esophagus-Muscularis          |
|          | −0.41       | \( 2.50 \times 10^{-8} \)  | Spleen                        |
|          | −0.38       | \( 4.50 \times 10^{-8} \)  | Colon-Sigmoid                 |
|          | −0.38       | \( 2.90 \times 10^{-7} \)  | Small Intestine-Terminal Ileum|
|          | −0.28       | \( 3.80 \times 10^{-7} \)  | Stomach                       |
|          | −0.29       | \( 4.10 \times 10^{-7} \)  | Esophagus-Gastroesophageal Junction|
|          | −0.35       | \( 8.90 \times 10^{-7} \)  | Pancreas                      |
| rs1682111| −0.34       | \( 9.30 \times 10^{-6} \)  | Small Intestine-Terminal Ileum|
|          | −0.3        | \( 2.50 \times 10^{-5} \)  | Colon-Sigmoid                 |
| rs843752 | −0.35       | \( 1.30 \times 10^{-6} \)  | Colon-Sigmoid                 |
|          | −0.37       | \( 1.10 \times 10^{-5} \)  | Small Intestine-Terminal Ileum|
|          | −0.22       | \( 1.60 \times 10^{-5} \)  | Esophagus-Muscularis          |
| rs843645 | −0.42       | \( 1.00 \times 10^{-5} \)  | Small Intestine-Terminal Ileum|
| rs843711 | −0.28       | \( 2.10 \times 10^{-7} \)  | Esophagus-Mucosa              |
|          | −0.32       | \( 8.60 \times 10^{-6} \)  | Small Intestine-Terminal Ileum|
|          | −0.19       | \( 5.20 \times 10^{-5} \)  | Esophagus-Muscularis          |

### 3.5 The expression ACYP2 gene in digestive-related tissues

We further performed eQTL analysis to evaluate the effect of different genotypes on ACYP2 gene expression in the digestive tract by the GTEx dataset. We found that five SNPs (rs6713088, rs1682111, rs843752, rs843645, and rs843711) of ACYP2 were significantly expressed in the relevant tissues of the digestive tract (Table 4), hinted that these SNPs may affect the expression of ACYP2 in GI cancer. Especially the two SNPs (rs6713088 and rs843711) correlated with GI cancer risk as Figure 2 displayed, rs6713088 loci were significantly expressed in esophagus-mucosa (\( p = 3.10 \times 10^{-30} \)), colon-transverse (\( p = 1.10 \times 10^{-17} \)), stomach (\( p = 3.80 \times 10^{-7} \)), and whole blood (\( p = 5.90 \times 10^{-8} \)); rs843711 was significantly expressed in esophagus-mucosa (\( p = 2.10 \times 10^{-7} \)) and esophagus-muscularis (\( p = 5.20 \times 10^{-5} \)).

### 4 DISCUSSION

In our case-control study, we determined the contributions of ACYP2 gene SNPs to GI cancer. We identified that rs6713088, rs843711, and rs11896604 in the ACYP2 gene

**TABLE 4** The expression in ACYP2 gene in the relevant tissues of the digestive tract
associated with an increased risk of GI cancer, suggesting an association between genetic polymorphism of ACYP2 and the susceptibility of GI cancer.

In our research, we found that ACYP2 rs6713088 increased risk of GI cancer. In liver cancer (Chen et al., 2017), rs6713088 G allele increased the risk of liver cancer compared with the C allele carriers (OR = 1.27). Meanwhile, rs6713088 G allele also promoted the risk of gastric cancer (OR = 1.30) (Li et al., 2017). In colorectal cancer, G allele is also a risk factor for colorectal cancer (Liu, Zhang, et al., 2017). These results are similar to our results. For rs843711 loci, Liang et al. (2017) found that the mutation of rs843711 was associated with colorectal cancer. Rs843711 risk allele “T” frequency in case and control had a significant difference and the variant increased the gastric cancer risk (Li et al., 2017). These results are similar to our results. Therefore, we believe that the ACYP2 gene is a risk factor for GI.

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). By UALCAN database (http://ualcan.path.uab.edu/index.html), we found that there were differences in the expression of ACYP2 gene in liver different tumor stages and esophageal carcinoma. And by Kaplan–Meier Plotter analysis (http://kmplot.com/analysis/index.php?p=service&cancer=gastric; http://www.oncolnc.org/; http://ualcan.path.uab.edu/index.html), patients with high expression have higher survival rates than patients with low expression (Gastric cancer, liver patients); while in esophageal carcinoma, highly expressed patients have low survival rates. Furthermore, results of the GTEx database revealed an eQTL of rs6713088 and rs843711 that affect the expression
of ACYP2 gene. Therefore, we believe that the ACYP2 gene influence the occurrence and development of the GI.

In conclusion, the present study is an attempt to investigate genetic association for genes ACYP2. Our results show an association between ACYP2 gene polymorphism and GI cancer in Chinese Han population. The results of this study might be helpful to understanding the important function of ACYP2 in GI cancer development and in developing drugs to treat GI cancer. However, further studies are warranted on larger patients from other ethnic groups to confirm our results. Further clarify the role of these two genes in the development of Liver cancer.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

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

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