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Association between *ACYP2* polymorphisms and the risk of renal cell cancer

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Abstract

Background: Kidney cancer is the predominant form of malignancy of the kidney and accounts for approximately 3%–4% of all cancers. Renal cell cancer (RCC) represents more than 85% of kidney cancer. It has been reported that genetic factors may predispose individuals to RCC. This study evaluated the association between Acylphosphatase 2 (*ACYP2*) gene polymorphisms and RCC risk in the Han Chinese population.

Methods: Twelve single-nucleotide polymorphisms (SNPs) in *ACYP2* were genotyped using the Agena MassARRAY platform from 293 RCC patients and 495 controls. The Chi-squared test, genetic models, haplotype, and stratification analyses were used to evaluate the association between SNPs and the risk of RCC. The relative risk was estimated using the odds ratio (OR) and 95% confidence interval (CI).

Results: We observed that the rs6713088 allele G (OR = 1.26, 95% CI: 1.03–1.53, p = .023) and rs843711 allele T (OR = 1.29, 95% CI: 1.06–1.57, p = .010) were associated with increased RCC risk. Genetic model analyses found that rs843711 was significantly associated with an increased RCC risk under the recessive model and log-additive model after adjusting for age and gender. Haplotype analysis showed that the haplotype "TTCTCGCC" (OR = 0.67, 95% CI: 0.48–0.94, p = .021) was associated with a decreased risk of RCC in the Han Chinese population. Stratification analysis also found that rs6713088 and rs843711 were significantly associated with increased RCC risk.

Conclusion: In summary, the results suggested that *ACYP2* polymorphisms could be used as a genetic marker for RCC. Additional functional and association studies are required to validate our results.

KEYWORDS

ACYP2, case-control, Chinese Han, polymorphism, renal cell cancer

Yuhe Wang and Yongtong Zhang are joint first authors.

1 | INTRODUCTION

Kidney cancer is the predominant form of malignancy of the kidney and accounts for approximately 3%–4% of all cancers (Torre et al., 2015). An estimation of the worldwide incidence and mortality of 27 cancers reported that approximately 403,262 (2.2% of the total cases) new kidney cancer cases were diagnosed and 175,098 individuals died from kidney cancer (1.8 of the total cancer deaths) in 2018. Renal cell cancer (RCC) represents more than 85% of kidney cancer, and clear cell renal carcinoma is the most common type of RCC. Many epidemiological studies have found a number of predisposing conditions related to the development of RCC, such as cigarette smoking, alcohol intake, obesity, hypertension, and diabetes (Chow, Dong, & Devesa, 2010). Although many subjects are exposed to these risk factors during their lifetime, only some individuals develop RCC, which suggests that genetic susceptibility may play a role in the etiology of RCC. Several studies indicate that the tumorigenesis of RCC involves a complex process determined by environmental and genetic factors as well as interactions between these factors (Semenza, Ziogas, Largent, Peel, & Anton-Culver, 2001). Previous studies report that genetic polymorphisms in some genes are associated with a risk of RCC, such as *IL-16* (Yang, Chen, Zhang, Sun, & Chen, 2015) and *VDR* (Yang et al., 2016).

ACYP2 is located on chromosome 2p16.2 and encodes the small cytosolic enzyme Acylphosphatase, which can hydrolyze the phosphoenzyme intermediates of different membrane pumps, particularly the Ca^{2+}/Mg^{2+}-ATPase from the sarcoplasmic reticulum of skeletal muscle. These enzymes can adjust the stability of the inner environment through calcium ion transport (Degl'Innocenti et al., 1999). Previous studies show that *ACYP2* overexpression promotes the differentiation of SH-SY5Y neuroblastoma cells (Cecchi et al., 2004). *ACYP2* is associated with colorectal cancer metastasis (Riley, Macnab, Farrell, & Cohn, 1997). A genome-wide meta-analysis study demonstrated that a single-nucleotide polymorphism (SNP) (rs11125529) in *ACYP2* is significantly associated with telomere length (Codd et al., 2013). Interestingly, telomere length is associated with RCC risk and survival (Pal et al., 2015; Svenson, Ljungberg, & Roos, 2009).

Some studies indicated that the *ACYP2* polymorphisms were associated with breast cancer (Liu et al., 2016; Zhang et al., 2016), colorectal cancer (Fang et al., 2016), lung cancer (Chen et al., 2016), gastric cancer (Li et al., 2017), and liver cancer (Chen et al., 2017). However, there are no previous reports examining the role of *ACYP2* polymorphisms in the risk of RCC. The mRNA expression level of *ACYP2* is significantly different between normal and kidney renal clear cell carcinoma samples based on major cancer stages, gender, and tumor grade from the UALCAN database, as shown in Figure 1 (http://ualcan.path.uab.edu/cgi-bin/ualcan-res.pl). *ACYP2* low expression is associated with better survival in kidney renal clear cell carcinoma from the OncoLnc database, as shown in Figure 2 (http://www.oncolnc.org/). We hypothesized that *ACYP2* polymorphisms are associated with the risk of RCC. To test this hypothesis, we conducted a case-control study to evaluate the association between 12 SNPs (rs6713088, rs12621038, rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, rs11896604, rs17045754, and rs843720) reported in previous studies (Chen et al., 2016, 2017; Fang et al., 2016; He et al., 2016; Li et al., 2017; Liang et al., 2016; Liu et al., 2016; Zhang et al., 2016) and the risk of RCC in the Chinese Han population.

2 | MATERIALS AND METHODS

2.1 | Study subjects

This study included 293 RCC patients and 495 unrelated healthy control subjects. The RCC patients were recruited from the First Affiliated Hospital of Xi'an Jiaotong University. The controls were randomly selected from individuals who requested general health examinations in the same hospital during the same period without any cancer history. All the individuals included in the study are ethnic Han Chinese with no genetic relationship, and their ancestors lived in the region for at least three generations. All the patients were newly diagnosed with histopathologically confirmed RCC. Patients who received chemotherapy or radiotherapy before surgery or had another

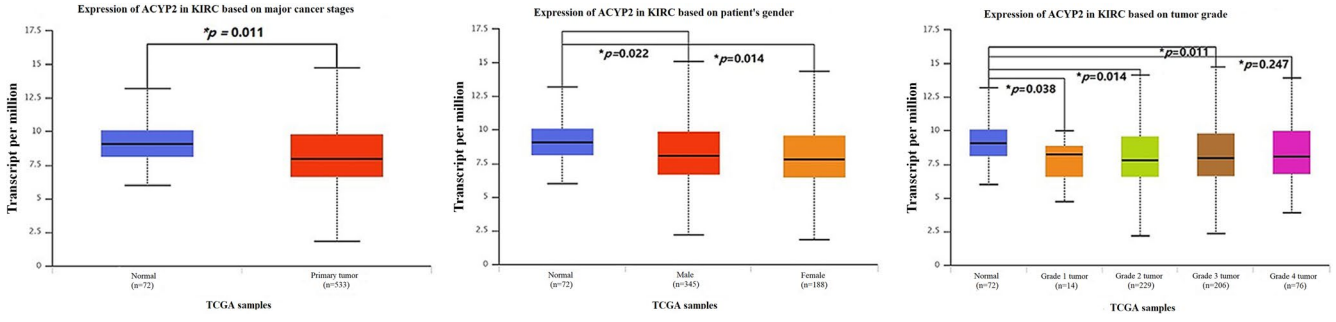

FIGURE 1 mRNA expression level of *ACYP2* between normal and KIRC samples. KIRC, kidney renal clear cell carcinoma

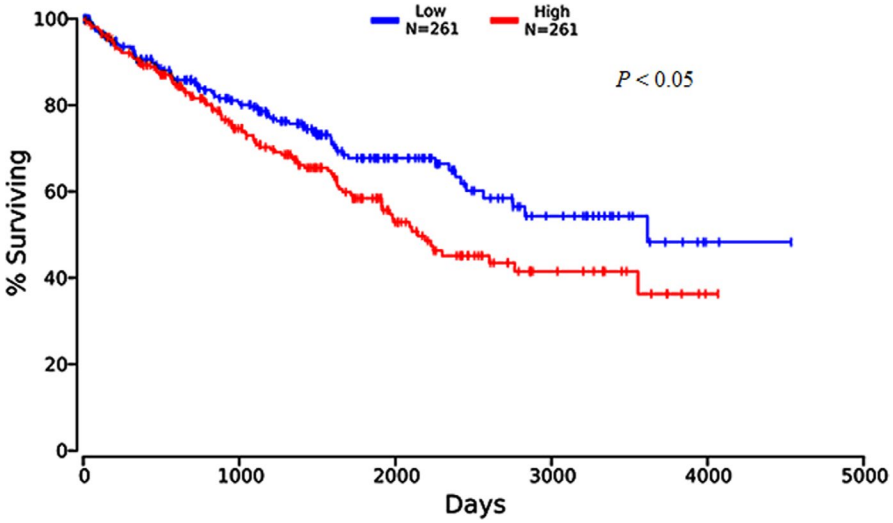

FIGURE 2 *ACYP2* low expression is associated with better survival in kidney renal clear cell carcinoma Kaplan–Meier plots of overall survival: comparison of patients with high versus low expression of *ACYP2* in kidney renal clear cell carcinoma patients (http://www.oncolnc.org/)

type of cancer were excluded from the study. All the patients were recruited without age, sex, or disease stage restrictions.

2.2 | Ethical approval

The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Each participant signed a written informed consent form prior to enrollment. This study conformed to the standards of the Declaration of Helsinki.

2.3 | DNA extraction

Peripheral venous blood samples were collected from both RCC patients and controls using vacutainer tubes containing EDTA. Genomic DNA was isolated from the blood samples using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd.) following the manufacturer's instructions. DNA concentration and purity were evaluated using a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific).

2.4 | SNPs selection and genotyping

Twelve SNPs (rs6713088, rs12621038, rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, rs11896604, rs17045754, and rs843720) in *ACYP2* screened in previous research (Chen et al., 2016; Chen et al., 2017; Fang et al., 2016; He et al., 2016; Li et al., 2017; Liang et al., 2016; Liu et al., 2016; Zhang et al., 2016) at a minor allele frequency (MAF) > 5% in the global population were examined in our study. The amplification and extension SNP primers were designed using the Agena Bioscience Assay Design Suite V2.0 software (https://agenacx.com/online-tools/). The sequences of primers corresponding to each SNP are shown in Table 1. These polymorphisms were genotyped using the Agena MassARRAY platform with iPLEX gold chemistry (Agena Bioscience) according to the standard protocol recommended by the manufacturer. Agena Bioscience TYPER version 4.0 software was used for data management and analysis.

2.5 | Statistical analysis

The Hardy–Weinberg equilibrium (HWE) of each SNP was assessed for the genotype frequencies in the control patients through an exact test. The allele frequencies between the RCC patients and controls were compared using a Chi-squared test, and the relative risk was estimated through an odds ratio (OR) and a 95% confidence interval (CI). Subsequently, we evaluated genetic polymorphisms of *ACYP2* and RCC susceptibility under four genetic models (codominant, dominant, recessive, and log-additive) using the SNPStats software platform (https://www.snpstats.net/start.htm) (San Francisco et al., 2014; Sole, Guino, Valls, Iniesta, & Moreno, 2006). Haploview software version 4.2 was used for the analysis of linkage disequilibrium (LD) and haplotype construction. The association between haplotypes and RCC risk was evaluated using PLINK software (Version 1.07). All statistical analyses were performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL). We considered p values <.05 to be statistically significant and all statistical tests were two-sided.

3 | RESULTS

The characteristics of all study participants are presented in Table 2. This study included 293 RCC patients (100 females and 193 males) and 495 (315 females and 180 males) healthy controls. The average ages of the cases and controls were

TABLE 1 The primer sequences for single-nucleotide polymorphisms in *ACYP2* polymerase chain reaction and single-base extension reaction

SNP-ID	2nd–PCRP	1st–PCRP	UEP-SEQ
rs6713088	ACGTTGGATGGTCACCAAAACACGTAATG	ACGTTGGATGACACACACAGACTCCTTCAC	gaggcCAGAATGGTCCACTAGAGA
rs12621038	ACGTTGGATGGGCATAAGTTTTATTGCCTC	ACGTTGGATGATTGTGCTAGGCACTTTAGG	ccATTGCCTCAGCTAGACT
rs1682111	ACGTTGGATGGCCAGTGGGAATGCAAAATG	ACGTTGGATGGAATTGCTGGGTTATTTGGC	tgtcATGCAAAATGAAACAGACACTT
rs843752	ACGTTGGATGGAGACAACATAATGGAGGTC	ACGTTGGATGTCCTCTTTTCAGAAACCTGC	cGAGTTTGGGTTTGAGGT
rs10439478	ACGTTGGATGCTACACTCTCCAGAGGAATG	ACGTTGGATGTAGCACAAGACCTACACTGG	TTGCTGTTTTCCCAGAA
rs843645	ACGTTGGATGACAGTGCCTTTAGCAAGGTG	ACGTTGGATGGAAATCTGAATACCACCTAC	TCATAGGCACTACTGTATC
rs11125529	ACGTTGGATGCCGAAGAAAAGAAGATGAC	ACGTTGGATGGAGCTTAGTTGTTTACAGATG	AGAAAAGAAGATGACTAAAACAT
rs12615793	ACGTTGGATGATCTTGGCCCTTGAAGAA	ACGTTGGATGTTTGAGCTTAGTTGTTTAC	AAATTGAGTGACAAATATAAACTAC
rs843711	ACGTTGGATGTGCCTTGTGGGAATTAGAGC	ACGTTGGATGGACAAAGGACCTTACAACTC	gggaTCAGGGAACCAGTGCAAA
rs11896604	ACGTTGGATGTGTCTCTGACCTAGCATGTA	ACGTTGGATGAAGTCAGAATAGTGCTTAC	GTTAAGCTTGCAAGGAG
rs17045754	ACGTTGGATGGAAATCAGGGATATTAGTGC	ACGTTGGATGCTGTAAAAGTTCTGGCATGG	caggTATTCAGCTTCCTAGAGTTA
rs843720	ACGTTGGATGAGTCAGAGCTAGACCTCTGG	ACGTTGGATGCTTCACAACACTCCTGTAAG	ccccAATCTGTCTCAGGGTCTT

Note: Sequences are written in the 5′ → 3′ (left to right) orientation.
Abbreviations: PCRP, Polymerase chain reaction primer; SNP, Single-nucleotide polymorphism; UEP, unique base extension primer.

56.9 years and 54.5 years, respectively. The mean body mass index (BMI) of the cases and controls was 23.4 kg/m^2 and 23.1 kg/m^2, respectively. There were significant differences in age, gender, smoking, and drinking between the RCC case and control groups ($p < .05$). To eliminate residual confounding effects, the variables of age, gender, and BMI were adjusted in the later logistic regression analysis.

The basic information of the selected SNPs and the associations with RCC risk are summarized in Table 3, including band, position, role, alleles (A/B), HWE-*P*, and MAF (case and control). The genotype frequencies of rs843720 in the control group did not conform to HWE ($p < .05$); therefore, that polymorphism was excluded from further analysis. The frequency of the rs6713088 G allele in the cases (45.3%) was higher than that in the controls (39.7%) and had a significantly increased susceptibility to RCC (OR = 1.26, 95% CI: 1.03–1.53, $p = .023$). Meanwhile, the T allele of rs843711 was also associated with an increased risk of RCC (OR = 1.29, 95% CI: 1.06–1.57, $p = .010$).

Genetic model analyses found that rs843711 was associated with a 1.52-fold increase in the risk of RCC under the recessive model (OR = 1.52, 95% CI: 1.06–2.18, $p = .025$) and rs843711 was associated with a 1.31-fold increased risk of RCC under the log-additive model (OR = 1.31, 95% CI: 1.05–1.63, $p = .017$) after adjusting for age and gender, as shown in Table 4.

Strong LD was observed between each pair of eight SNPs (rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, and rs11896604) in *ACYP2*, as shown in Figure 3. The results of the association between the haplotypes and RCC risk are listed in Table 5. We found that the haplotype "TTCTCGCC" was associated with a decreased risk of RCC after adjusting for age and gender (OR = 0.67, 95% CI: 0.48–0.94, $p = .021$).

In Table 6, stratification analysis showed that rs6713088 also significantly increased the risk of RCC for those ≥ 55 years (OR = 1.33, 95% CI: 1.02–1.75, $p = .037$), smoking (OR = 1.59, 95% CI: 1.01–2.51, $p = .047$), and no drinking groups (OR = 1.42, 95% CI: 1.06–1.88, $p = .017$). We also found that rs843711 significantly increased the risk of RCC for ages ≥ 55 years (OR = 1.38, 95% CI: 1.05–1.80, $p = .019$), no smoking (OR = 1.47, 95% CI: 1.09–1.99, $p = .012$), smoking (OR = 1.90, 95% CI: 1.21–3.00, $p = .005$), no drinking (OR = 1.53, 95% CI: 1.15–2.02, $p = .003$), and I/II stage (OR = 1.29, 95% CI: 1.04–1.60, $p = .023$) groups.

4 | DISCUSSION

This study evaluated the association between *ACYP2* polymorphisms and the risk of RCC in the Han Chinese population. Our results showed that rs6713088 and rs843711 were associated with increased risk of RCC and the haplotype

TABLE 2 Characteristics of renal cell cancer cases and healthy controls

Variable	Case *N* (%)	Control *N* (%)	*p*
Total	293	495	
Age (Mean ± *SD*) years	56.9 ± 11.7	54.5 ± 9.4	.002[a]
BMI (Mean ± *SD*) kg/m^2	23.4 ± 4.7	23.1 ± 3.2	.311[a]
Gender			<.001[b]
Female	100 (34.1)	315 (63.6)	
Male	193 (65.9)	180 (36.4)	
Smoking			<.001[b]
–		264 (53.3)	
No	173 (59.0)	172 (34.7)	
Yes	120 (41.0)	59 (11.9)	
Drinking			<.001[b]
–		264 (53.3)	
No	240 (81.9)	172 (34.7)	
Yes	53 (18.1)	59 (11.9)	

Note: p^a values were calculated using Welch's *t* test (two-sided).
p^b values were calculated using Pearson's Chi-squared test (two-sided).
$p < .05$ indicates statistical significance.

"TTCTCGCC" (rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711, and rs11896604) had a statistically significant reduced susceptibility to RCC. In addition, stratification analysis found that rs6713088 and rs843711 significantly increased the risk of RCC.

The pathogenesis of RCC is not clear. Previous reports indicate that *ACYP2* can adjust the stability of the inner environment of Ca^{2+}. Ca^{2+} homeostasis is the first sign of apoptosis (Sawant, Dasgupta, Lavhale, & Sitasawad, 2016) that can regulate cell survival and death (Hajnoczky, Davies, & Madesh, 2003). Cancer cells can prevent calcium flow by reducing the expression of Ca^{2+} channels, gaining resistance to long-term endoplasmic reticulum calcium deficiency, and downregulating the mitochondrial calcium unidirectional transporter, which prevents apoptosis (Pinton, Giorgi, Siviero, Zecchini, & Rizzuto, 2008). In addition, *ACYP2* is associated with telomere length, which is crucial for maintaining chromosome integrity and genomic stability (Blackburn, 2010), but a critically short telomere length can initiate the process of carcinogenesis (Cheung & Deng, 2008). We know that apoptosis plays an important role in the development of tumors. Therefore, *ACYP2* mutations may affect telomere length and regulate apoptosis as well as further promote tumorigenesis.

Although rs11125529 is significantly associated with telomere length (Codd et al., 2013), no significant association was found between rs11125529 and RCC risk in this study. The *ACYP2* polymorphisms were previously reported to be associated with cancers risk, as shown in Table 7. Our results showed that rs6713088 was significantly associated with an increased risk of RCC. Other studies found that rs6713088 was also associated with increased risk of colorectal cancer (OR = 1.75, 95% CI: 1.03–2.97, $p = .038$) (Fang et al., 2016),

TABLE 3 The single-nucleotide polymorphisms and the associations with renal cell cancer risk

SNP-ID	Position	Alleles A/B	HWE-*p*[a]	MAF		OR	95% CI		*p*[b]
				Case	Control				
rs6713088	54345469	G/C	.778	0.438	0.397	1.26	1.03	1.53	.023
rs12621038	54391113	T/C	.786	0.426	0.458	0.88	0.72	1.07	.187
rs1682111	54427979	A/T	.832	0.307	0.303	0.99	0.80	1.23	.946
rs843752	54446587	G/T	.569	0.295	0.269	1.18	0.95	1.47	.127
rs10439478	54459450	C/A	.927	0.396	0.431	0.86	0.70	1.05	.133
rs843645	54474664	G/T	1.000	0.292	0.261	1.20	0.97	1.50	.094
rs11125529	54475866	A/C	.092	0.211	0.180	1.21	0.95	1.55	.120
rs12615793	54475914	A/G	.042	0.225	0.191	1.23	0.97	1.57	.088
rs843711	54479117	T/C	.124	0.510	0.454	1.29	1.06	1.57	.010
rs11896604	54479199	G/C	.249	0.219	0.194	1.19	0.93	1.51	.162
rs17045754	54496757	C/G	.297	0.205	0.185	1.14	0.89	1.46	.285
rs843720	54510660	T/G	.000	0.339	0.540	2.34	1.91	2.86	.000

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.
$p < .05$ indicates statistical significance.
[a]*p* values were calculated using exact test.
[b]*p* values were calculated from Pearson's Chi-squared test (two-sided).

gastric cancer (OR = 1.30, 95% CI: 1.03–1.64, $p = .024$) (Li et al., 2017), and liver cancer (OR = 1.27, 95% CI: 1.07–1.52, $p = .007$) (Chen et al., 2017). In addition, rs843711 also exhibited an increased risk of RCC both under the recessive and log-additive model. Previous association studies observed that rs843711 was associated with an increased risk of

TABLE 4 Genetic model analyses of the association between *ACYP2* polymorphisms and the risk of renal cell cancer (adjusted for gender, age, and BMI)

SNP-ID	Model	Genotype	Case (%)	Control (%)	OR (95% CI)	*p*
rs6713088	Codominant	C/C	91 (31.3%)	178 (36%)	1	.390
		C/G	145 (49.8%)	240 (48.6%)	1.17 (0.83–1.65)	
		G/G	55 (18.9%)	76 (15.4%)	1.35 (0.86–2.12)	
	Dominant	C/C	91 (31.3%)	178 (36%)	1	.230
		C/G–G/G	200 (68.7%)	316 (64%)	1.22 (0.88–1.68)	
	Recessive	C/C–C/G	236 (81.1%)	418 (84.6%)	1	.310
		G/G	55 (18.9%)	76 (15.4%)	1.23 (0.82–1.84)	
	Log-additive	—	—	—	1.17 (0.94–1.45)	.170
rs12621038	Codominant	C/C	95 (32.6%)	146 (29.6%)	1	.510
		T/C	144 (49.5%)	242 (49.1%)	0.91 (0.64–1.29)	
		T/T	52 (17.9%)	105 (21.3%)	0.77 (0.49–1.20)	
	Dominant	C/C	95 (32.6%)	146 (29.6%)	1	.410
		T/C–T/T	196 (67.3%)	347 (70.4%)	0.87 (0.63–1.21)	
	Recessive	C/C–T/C	239 (82.1%)	388 (78.7%)	1	.300
		T/T	52 (17.9%)	105 (21.3%)	0.82 (0.55–1.20)	
	Log-additive	—	—	—	0.88 (0.71–1.10)	.260
rs1682111	Codominant	T/T	141 (48.3%)	239 (48.3%)	1	.650
		T/A	123 (42.1%)	212 (42.8%)	0.89 (0.65–1.23)	
		A/A	28 (9.6%)	44 (8.9%)	1.10 (0.64–1.90)	
	Dominant	T/T	141 (48.3%)	239 (48.3%)	1	.610
		T/A–A/A	151 (51.7%)	256 (51.7%)	0.92 (0.68–1.25)	
	Recessive	T/T–T/A	264 (90.4%)	451 (91.1%)	1	.560
		A/A	28 (9.6%)	44 (8.9%)	1.17 (0.69–1.97)	
	Log-additive	—	—	—	0.98 (0.78–1.24)	.890
rs843752	Codominant	T/T	146 (50%)	262 (52.9%)	1	.450
		G/T	120 (41.1%)	200 (40.4%)	1.12 (0.82–1.55)	
		G/G	26 (8.9%)	33 (6.7%)	1.42 (0.79–2.53)	
	Dominant	T/T	146 (50%)	262 (52.9%)	1	.320
		G/T–G/G	146 (50%)	233 (47.1%)	1.17 (0.86–1.58)	
	Recessive	T/T–G/T	266 (91.1%)	462 (93.3%)	1	.300
		G/G	26 (8.9%)	33 (6.7%)	1.35 (0.77–2.36)	
	Log-additive	—	—	—	1.16 (0.91–1.47)	.220
rs10439478	Codominant	A/A	107 (36.6%)	160 (32.5%)	1	.400
		C/A	139 (47.6%)	241 (48.9%)	0.82 (0.59–1.16)	
		C/C	46 (15.8%)	92 (18.7%)	0.76 (0.48–1.20)	
	Dominant	A/A	107 (36.6%)	160 (32.5%)	1	.190
		C/A-C/C	185 (63.4%)	333 (67.5%)	0.81 (0.59–1.11)	
	Recessive	A/A-C/A	246 (84.2%)	401 (81.3%)	1	.440
		C/C	46 (15.8%)	92 (18.7%)	0.85 (0.57–1.28)	
	Log-additive	—	—	—	0.86 (0.69–1.08)	.190

(Continues)

TABLE 4 (Continued)

SNP-ID	Model	Genotype	Case (%)	Control (%)	OR (95% CI)	*p*
rs843645	Codominant	T/T	145 (49.8%)	270 (54.5%)	1	.340
		G/T	122 (41.9%)	192 (38.8%)	1.23 (0.90–1.70)	
		G/G	24 (8.2%)	33 (6.7%)	1.34 (0.74–2.42)	
	Dominant	T/T	145 (49.8%)	270 (54.5%)	1	.150
		G/T-G/G	146 (50.2%)	225 (45.5%)	1.25 (0.92–1.69)	
	Recessive	T/T-G/T	267 (91.8%)	462 (93.3%)	1	.490
		G/G	24 (8.2%)	33 (6.7%)	1.22 (0.69–2.17)	
	Log-additive	—	—	—	1.19 (0.94–1.51)	.150
rs11125529	Codominant	C/C	183 (62.7%)	327 (66.1%)	1	.140
		C/A	95 (32.5%)	158 (31.9%)	1.10 (0.79–1.53)	
		A/A	14 (4.8%)	10 (2%)	2.37 (0.99–5.65)	
	Dominant	C/C	183 (62.7%)	327 (66.1%)	1	.300
		C/A-A/A	109 (37.3%)	168 (33.9%)	1.18 (0.86–1.62)	
	Recessive	C/C-C/A	278 (95.2%)	485 (98%)	1	.058
		A/A	14 (4.8%)	10 (2%)	2.29 (0.97–5.43)	
	Log-additive	—	—	—	1.24 (0.94–1.63)	.130
rs843711	Codominant	C/C	69 (23.6%)	139 (28.1%)	1	.050
		C/T	148 (50.7%)	263 (53.1%)	1.20 (0.83–1.74)	
		T/T	75 (25.7%)	93 (18.8%)	1.71 (1.10–2.66)	
	Dominant	C/C	69 (23.6%)	139 (28.1%)	1	.100
		C/T-T/T	223 (76.4%)	356 (71.9%)	1.34 (0.94–1.90)	
	Recessive	C/C-C/T	217 (74.3%)	402 (81.2%)	1	.025
		T/T	75 (25.7%)	93 (18.8%)	1.52 (1.06–2.18)	
	Log-additive	—	—	—	1.31 (1.05–1.63)	.017
rs11896604	Codominant	C/C	178 (61%)	317 (64%)	1	.370
		C/G	100 (34.2%)	164 (33.1%)	1.15 (0.83–1.59)	
		G/G	14 (4.8%)	14 (2.8%)	1.66 (0.75–3.70)	
	Dominant	C/C	178 (61%)	317 (64%)	1	.270
		C/G-G/G	114 (39%)	178 (36%)	1.19 (0.87–1.63)	
	Recessive	C/C-C/G	278 (95.2%)	481 (97.2%)	1	.250
		G/G	14 (4.8%)	14 (2.8%)	1.58 (0.72–3.49)	
	Log-additive	—	—	—	1.20 (0.92–1.57)	.180
rs17045754	Codominant	G/G	183 (62.7%)	325 (65.7%)	1	.440
		G/C	98 (33.6%)	157 (31.7%)	1.15 (0.83–1.60)	
		C/C	11 (3.8%)	13 (2.6%)	1.60 (0.67–3.80)	
	Dominant	G/G	183 (62.7%)	325 (65.7%)	1	.290
		G/C-C/C	109 (37.3%)	170 (34.3%)	1.19 (0.86–1.63)	
	Recessive	G/G-G/C	281 (96.2%)	482 (97.4%)	1	.340
		C/C	11 (3.8%)	13 (2.6%)	1.53 (0.65–3.60)	
	Log-additive	—	—	—	1.19 (0.90–1.57)	.22

Abbreviations: 95% CI, 95% Confidence interval; OR, Odds ratio; SNP, Single-nucleotide polymorphism.
$p < .05$ indicates statistical significance.

colorectal cancer (OR = 1.38, 95% CI: 1.08–1.75, $p = .009$) (Fang et al., 2016), gastric cancer (OR = 1.40, 95% CI: 1.12–1.76, $p = .004$) (Li et al., 2017), and liver cancer (OR = 1.29, 95% CI: 1.09–1.54, $p = .004$) (Chen et al., 2017). The SNPs rs12621038, rs1682111, rs17045754, rs11896604, rs843706, and rs11125529 were previously reported to be associated

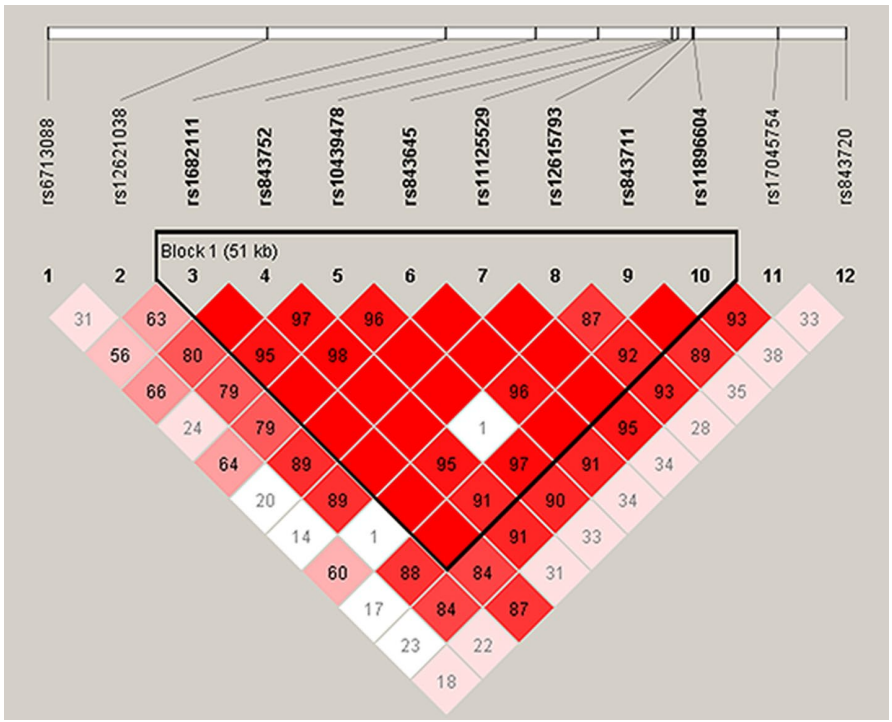

FIGURE 3 Haplotype block map for the 12 single-nucleotide polymorphisms in *ACYP2*. The linkage disequilibrium (LD) between each pair of SNPs is standardized deviation (D′). The bright red corresponds to a very strong LD, white corresponds to no LD, and pink corresponds to intermediate LD

TABLE 5 Association between the haplotypes and renal cell cancer risk (adjusted for gender, age, and BMI)

SNPs	Haplotype	F_A	F_U	Chi-squared	p^a	OR (95% CI)	p^b
rs1682111|rs843752|rs10439478|rs843645|rs11125529|rs12615793|rs843711|rs11896604	ATATCGCC	0.310	0.297	0.26	.607	1	—
	TGAGCGTC	0.281	0.253	1.31	.253	1.12 (0.84–1.49)	.440
	TTCTCGCC	0.137	0.219	13.84	.000	0.67 (0.48–0.94)	.021
	TTCTAATG	0.213	0.179	2.43	.119	1.16 (0.84–1.61)	.360
	TTCTCACC	0.017	0.011	0.77	.379	1.30 (0.51–3.29)	.590
	TTCTCGTG	0.008	0.011	0.27	.602	1.16 (0.39–3.47)	.790

Abbreviations: 95% CI, 95% Confidence interval; F_A, Frequency in cases; F_U, Frequency in controls; OR, Odds ratio; SNP, Single-nucleotide polymorphism.
p^a values were calculated using Pearson's Chi-squared test.
p^b values were calculated using the Wald test.
$p < .05$ indicates statistical significance.

TABLE 6 Stratification analysis between rs6713088, rs843711, and renal cell cancer risk

	rs6713088				rs843711			
Variable	MAF-case	MAF-control	OR (95% CI)	*p*	MAF-case	MAF-control	OR (95% CI)	*p*
<55	0.422	0.422	1.00 (0.73–1.38)	.992	0.497	0.476	0.92 (0.27–1.26)	.589
≥55	0.380	0.450	1.33 (1.02–1.75)	.037	0.421	0.500	1.38 (1.05–1.80)	.019
No smoking	0.355	0.425	1.34 (0.99–1.83)	.059	0.413	0.509	1.47 (1.09–1.99)	.012
Smoking	0.347	0.458	1.59 (1.01–2.51)	.047	0.356	0.513	1.90 (1.21–3.00)	.005
No drinking	0.355	0.438	1.42 (1.06–1.88)	.017	0.410	0.515	1.53 (1.15–2.02)	.003
Drinking	0.347	0.442	1.49 (0.87–2.56)	.149	0.364	0.491	1.68 (0.98–2.87)	.056
I/II stage	0.397	0.450	1.25 (1.00–1.55)	.051	0.454	0.517	1.29 (1.04–1.60)	.023
III/IV stage	0.397	0.378	0.92 (0.60–1.41)	.711	0.454	0.480	1.11 (0.73–1.68)	.621

Abbreviations: 95% CI, 95% Confidence interval; MAF, minor allele frequency; OR, odds ratio.
$p < .05$ indicates statistical significance.

TABLE 7 Association *ACYP2* polymorphisms with cancer risk from previous studies

Cancers	SNP	Model	OR (95% CI)	*p*	Reference
Breast cancer	rs11896604	Dominant	0.62 (0.41–0.96)	.031	Liu et al. (2016)
	rs843706	Recessive	1.71 (1.06–2.77)	.030	
	rs11125529	Codominant	0.61 (0.39–0.96)	.032	
	rs12621038	Allele	0.70 (0.52–0.94)	.016	Zhang et al. (2016)
	rs1682111	Allele	1.38 (1.01–1.89)	.045	
	rs17045754	Allele	0.66 (0.45–0.96)	.029	
Colorectal cancer	rs843711	Allele	1.38 (1.08–1.75)	.009	Fang et al. (2016)
	rs843706	Allele	1.36 (1.07–1.73)	.012	
	rs6713088	Codominant	1.75 (1.03–2.97)	.038	
Lung cancer	rs1682111	Recessive	1.55 (1.04–2.30)	.029	Chen et al. (2016)
	rs11896604	Codominant	0.74 (0.36–1.53)	.049	
	rs843720	Recessive	1.48 (1.02–2.15)	.040	
Gastric cancer	rs6713088	Allele	1.30 (1.03–1.64)	.024	Li et al. (2017)
	rs11125529	Allele	1.42 (1.07–1.89)	.016	
	rs12615793	Allele	1.39 (1.05–1.84)	.020	
	rs843711	Allele	1.40 (1.12–1.76)	.004	
	rs11896604	Allele	1.41 (1.06–1.87)	.018	
	rs843706	Allele	1.35 (1.07–1.69)	.011	
	rs17045754	Allele	1.38 (1.03–1.83)	.029	
Liver cancer	rs6713088	Allele	1.27 (1.07–1.52)	.007	Chen et al. (2017)
	rs1682111	Allele	0.77 (0.64–0.94)	.008	
	rs843711	Allele	1.29 (1.09–1.54)	.004	
	rs843706	Allele	1.30 (1.09–1.55)	.003	
	rs843645	Codominant	1.40 (1.07–1.82)	.014	
	rs843720	Codominant	0.64 (0.41–1.00)	.048	

Abbreviations: 95% CI, 95% Confidence interval; OR, Odds ratio; SNP, Single-nucleotide polymorphism.
$p < .05$ indicates statistical significance.

with the risk of breast cancer (Liu et al., 2016; Zhang et al., 2016). The SNPs rs1682111, rs11896604, and rs843720 were found to be associated with lung cancer risk (Chen et al., 2016). However, the association of rs6713088, rs843711, and other SNP loci with susceptibility to RCC had not been reported. Therefore, the association between the polymorphisms in the *ACYP2* and the risk of RCC should be verified in a large sample.

In addition, the incidence of RCC increases with age (Chow & Devesa, 2008). A previous study found that smoking may increase RCC risk through chronic tissue hypoxia due to carbon monoxide exposure (Sharifi & Farrar, 2006). In RCC, peripheral blood lymphocytes have a higher level of DNA damage induced by a tobacco-specific N-nitrosamine (Clague et al., 2009). A meta-analysis study (Bellocco et al., 2012) reported that alcohol drinking has a negative association with the risk of RCC through the effects of alcohol on insulin sensitivity (Kiechl et al., 1996). Stratification analysis also found that rs6713088 and rs843711 significantly increased the risk of RCC.

Several limitations should not be ignored in this study. First, the sample size is relatively small. Second, we did not measure telomere length or assess the association between telomere length and the risk of RCC. Third, we also did not perform functional analyses. Therefore, further study will be needed to verify the results with a larger sample size and more comprehensive analyses.

In summary, our results confirmed that rs6713088 and rs843711 were connected to a significantly increased risk of RCC, but the haplotype "TTCTCGCC" was associated with a decreased risk of RCC in the Han Chinese population. Our results provide a theoretical basis for further study of the association between telomere length-related gene (*ACYP2*) and the risk of RCC.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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