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Original Article

Relationship of SNP rs35767 in IGF-1 promoter region with susceptibility to colorectal cancer

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Abstract: In vitro and animal experiments demonstrate that IGF-1 appears to play a role in the development and growth of colorectal cancer and the function of free IGF-1 protein is mediated by IGF-1R. The IGF-1R system plays a critical role in promoting the normal development of cells and malignant transformation via the phosphatidylinositol 3-kinase (PI3)/AKTA and mitogen-activated protein kinase (MAPK) pathways. Different variants of the promoter of IGF-1 are involved in the risk of suffering from various diseases. The current study examined the relationship between IGF-1 rs35767 polymorphism and the risk of colorectal cancer (CRC) in a population from China. The genotypes of rs35767 polymorphism of the promoter region of IGF-1 were examined in 734 subjects: 367 patients with CRC and 367 healthy individuals by PCR. LDL and TC levels in colorectal cancer patients were significantly higher than those in the healthy control group (*P = 0.045 and 0.046, respectively*). Compared with CC genotype carriers, people with the CT genotype had a 1.39-fold higher risk of CRC (*OR = 1.399, 95% CI 1.029-1.901 P = 0.032*). There was no association between genotypes of rs35767 and the risk of CRC, after stratification according to gender. The patients who carried the T allele tend to have poor tissue differentiation. SNP rs35767 polymorphism associated with IGF-1 levels may be associated with susceptibility to colorectal cancer. People with the CT genotype may have a higher risk of CRC, and the patients who carried T allele tend to have poor tissue differentiation.

Keywords: Polymorphism, single nucleotide, insulin-like growth factor i, colorectal neoplasms, disease susceptibility

Introduction

In China, colorectal cancer (CRC) is the most common malignancy, following lung cancer and breast cancer, with an estimate of 376000 new cases and 191000 deaths for the year 2015 [1]. Colorectal cancer is the fourth most common malignancy and the second leading cause of cancer death in the United States [2]. The difference in the incidence of colorectal cancer in different parts of the world can be due to environmental factors, dietary differences, and genetic diversity. Genetic variations in different genes can affect the risk of colorectal cancer [3].

IGF-1 is a single-chain polypeptide encoded by chromosome 12, mainly synthesized in the liver and regulated by growth hormone. It is an essential growth factor for healthy growth and, when overexpressed, may act as an active mitogen, anti-apoptotic peptide, and angiogenic promoter [4]. IGF-1 appears to play a significant role in the development and progression of colorectal cancer. Su et al. proved that a high plasma concentration of IGF-1, increased the risk of colorectal cancer [5]. Chong et al. demonstrated significant variability in IGF-1 serum levels, which is genetically determined [6]. Many studies have shown that the variants rs35767 in the promoter region of IGF-1 are associated with the level of circulating IGF-1, implying that SNP rs35767 may be associated with susceptibility to colorectal cancer [7-10]. The data obtained from the HapMap database show that the allelic distribution of studied SNP rs35767 differed significantly between Asians and Caucasians. Compared with the Caucasian population, the frequency of rs35767 minor alleles in the Chinese population is about three times that of Caucasians (0.354 vs 0.115).

Table 1. Demographic data for healthy controls and CRC patients

Demographic data	Healthy controls Number (%)	CRC patients Number (%)	X^2/t	*P*-value
Samples	367	367	--	--
Age (years)				
Male	66.1±9.49	66.1±9.31	0.057[a]	0.955
Female	65.3±9.25	65.5±9.87	0.162[a]	0.872
Gender				
Male	229 (62.4%)	219 (59.7%)	0.573[b]	0.449
Female	138 (37.6%)	148 (40.3%)		
LDL	3.2±0.69	3.1±0.54	1.87[a]	0.061
TC	5.1±1.02	4.9±0.94	2.001[a]	0.046
TG	1.3±0.56	1.3±0.71	0.211[a]	0.833
Tumor site				
Rectum		247 (61.3%)		
Colon		120 (32.7%)		
Stage				
A		57 (15.5%)		
B		154 (42.1%)		
C		152 (41.4%)		
D		4 (1.00%)		
IGF-1 (ng/mL)				
CC	128.3±48.1	144.4±68.6	3.46[a]	0.001
CT	134.8±41.8	152.1±72.3	1.42[a]	0.048
TT	146.5±57.2	160.1±63.3	1.83[a]	0.08
P-trend	0.031	0.048		

[a]Based on independent sample t-test. [b]Based on chi-square test. Abbreviations: LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Given the mentioned points and the importance of IGF-1 in the onset and development of cancer, the current study was designed to examine the relationship between CRC and the promoter region rs35767 gene polymorphism.

Materials and methods

This study is a controlled case-control study, involving patients managed in the Tianjin Union Medical Center, between May 2011 and November 2015. In the present study, 367 patients with CRC and 367 healthy subjects as the controls were enrolled. All subjects of this study were from the same geographic region and limited to Han Chinese ethnicity. The control group was matched to the case group in terms of body weight, gender, and age. The control group was confirmed by physical examination and imaging tests that were negative for malignancy, cardiovascular disease, and diabetes. In the case group, the patients were histologically confirmed colorectal cancer. The pathological staging was carried out according to the TNM (tumor, node, metastases) system. This study was approved by the Ethics Committee of Tianjin Union Hospital, and all subjects enrolled in this study have signed the informed consent. For this purpose, 3 ml of the whole blood was drawn and then the whole blood was stored in a proper vial containing EDTA, conserved in a freezer, at -80°C. Clinical information of the patients, such as LDL, TC, stage of disease, tumor location, and degree of differentiation, was recorded.

DNA extraction

Genomic DNA was isolated from peripheral blood leukocytes using TIANamp Blood DNA Midi Kit (Tiangen Biotech, Beijing, China), according to the manufacturer's instructions. All isolated DNA samples were stored at -80°C until use.

Genotyping

Genotyping for rs35767 in the promoter region was done by PCR, and then we performed gene sequencing (ABI-3730XL, Applied Biosystems, Foster City, CA). The sequencing results were compared with reference sequences in NCBI. The forward and reverse primer sequences of the SNP rs35767 were designed according to NCBI. The fragment containing SNP rs35767 polymorphism was amplified using forward 5'-TTGGGCACATAGTAGAGCTCAC-3' and reverse 5'-CAAAAGCCCAGAGCAGACAT-3'.

Statistical analysis

Statistical analyses were performed using SPSS 20.0. Categorical variables were analyzed using a chi-square test. For intergroup comparisons, continuous normal distribution variables were analyzed by independent samples ANOVA and expressed as mean ± standard deviations. In the control group, the chi-square test was

Table 2. Genotype and allele frequency of rs35767 polymorphism in CRC patients and control group

	Control	CRC	OR[a]	*P*-value
Gender				
Male	229 (62.4%)	219 (59.7%)	1.12 (0.833-1.509)	0.449
Female	138 (37.6%)	148 (40.3%)	Reference (1.00)	
Codominant				
CC, n (%)	176 (48.0%)	149 (40.6%)	Reference (1.00)	
CT, n (%)	154 (42.0%)	180 (49.0%)	1.399 (1.029-1.901)	0.032
TT, n (%)	37 (10.0%)	38 (10.4%)	1.213 (0.734-2.005)	0.451
Dominant				
CC, n (%)	176 (48.0%)	149 (40.6%)	1.348 (1.007-1.806)	0.045
TT+CT, n (%)	191 (52.0%)	218 (59.4%)		
Recessive				
TT, n (%)	37 (10.0%)	38 (10.4%)	1.030 (0.639-1.661)	0.903
CC+CT, n (%)	330 (90.0%)	329 (89.6%)		
Allele				
C, n (%)	506 (68.9%)	478 (65.1%)	1.19 (0.956-1.478)	0.12
T, n (%)	228 (31.1%)	256 (34.9%)		

[a]OR = adjusted OR, adjusted for gender, age, LDL and TC.

used to assess the deviation of the genotype distribution of rs35767 from the Hardy-Weinberg equilibrium (HWE). Power calculation and sample size estimation were done by PS: Power and Sample Size Calculation (Homepage: http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSample Size). The parameters used were 367 healthy people, 367 CRC patients, and minor allele frequency (MAF) for the tested variants in CRC group. The power was calculated at 40.0%. Logistic regression models were used for calculating OR (95% confidence intervals) and *P*-values. A two-sided P<0.05 was considered significant.

Results

Characteristics of study subjects

This study included 367 colorectal cancer patients (247 with rectal cancer, 120 with colon cancer), and the colorectal cancer patients are mainly distributed in stages B and C (42.1% and 41.4%, respectively) (**Table 1**). Because controls were age- and sex-matched to cases, there were no significant differences between cases and healthy controls regarding age (*P>0.05*) and sex ratio (*P = 0.449*). The LDL and cholesterol (TC) level in the case group were higher than that in the control group, and the differences were significant (*P = 0.045 and 0.046, respectively*). IGF-1 levels of the three genotypes in the CRC group were higher than that of the control group (P<0.05). In the subjects with or without CRC, patients with T alleles had higher levels of circulating IGF-1 than patients who do not carry the T allele (P-trend <0.05).

Association between genotypes and CRC risk

Genotyping distributions and frequencies and association between the genotypes and colorectal cancer risk are summarized in **Table 2**. In the control group, the rs35767 genotype distributions were compatible with the Hardy-Weinberg equilibrium (χ^2 *= 1.670, P = 0.434*). As compared with CC genotype carriers, people with the CT genotype had a 1.39-fold higher risk of CRC (*OR = 1.399, 95% CI 1.029-1.901 P = 0.032*) (**Table 2**). Under the dominant model, TT+CT genotype frequency was significantly higher in the CRC group than the healthy control group (*OR = 1.348 95% CI = 1.007-1.806 P = 0.045*). However, under recessive model, CC+CT versus TT was not significant (P = 0.903). There was no significance associated with CRC and allele (P>0.05).

After stratification according to gender, no statistically significant difference was observed between genotypes of rs35767 and the risk of CRC, under codominant model, dominant model, and recessive model (**Table 3**).

In the current study, we found no significant correlation between disease stages, gender, tumor location and the distribution of all genotypes (*P>0.05*). However, patients with colorectal cancer who carry the t allele exhibited negative associations with degree of differentiation (P = 0.014) (**Table 4**).

Discussion

In the current study, we investigated the SNP rs35767 genotype from the promoter region

Table 3. Genotyping of IGF-1 gene SNP rs35767 in men and women patients

	Male				Female			
	Case (N = 219)	Control (N = 229)	OR (95% CI)	*P*-value	Case (N = 148)	Control (N = 138)	OR[a] (95% CI)	*P*-value
Codominant								
CC, n (%)	87 (39.7%)	109 (47.6%)	Reference (1.00)	–	62 (41.9%)	67 (48.6%)	Reference (1.00)	–
CT, n (%)	107 (48.9%)	97 (42.4%)	1.382 (0.932-2.049)	0.107	73 (49.3%)	57 (41.3%)	1.384 (0.849-2.257)	0.193
TT, n (%)	25 (11.4%)	23 (10.0%)	1.362 (0.732-2.563)	0.339	13 (8.80%)	14 (10.1%)	1.003 (0.437-2.302)	0.994
Dominant								
CC, n (%)	87 (39.7%)	109 (47.6%)	1.378 (0.947-2.005)	0.094	62 (41.9%)	67 (48.6%)	1.309 (0.821-2.088)	0.258
TT+CT, n (%)	132 (60.3%)	120 (52.4%)			86 (58.1%)	71 (51.4%)		
Recessive								
TT, n (%)	25 (11.4%)	23 (10.0%)	0.866 (0.476-1.578)	0.639	13 (8.80%)	14 (10.1%)	1.172 (0.530-2.592)	0.694
CC+CT, n (%)	194 (88.6%)	206 (90.0%)			135 (91.2%)	124 (89.9%)		
Allele								
C, n (%)	281 (64.2%)	315 (68.8%)	1.231 (0.932-1.625)	0.143	197 (66.6%)	191 (69.2%)	1.129 (0.795-1.605)	0.498
T, n (%)	157 (35.8%)	143 (31.2%)			99 (33.4%)	85 (30.8%)		

[a]OR = adjusted OR, adjusted for age, LDL and TC.

Table 4. Association between IGF-1 gene polymorphism and clinicopathological characteristics of CRC

Clinical characteristics	Genotype (N = 367)			Allele (N = 734)	
Gender	CC, n (%)	CT, n (%)	TT, n (%)	C, n (%)	T, n (%)
Male	87 (39.7%)	107 (48.9%)	25 (11.4%)	281 (64.2%)	157 (35.8%)
Female	62 (41.9%)	73 (49.3%)	13 (8.80%)	197 (66.6%)	99 (33.4%)
(χ^2/P)		0.697/0.706		0.447/0.504	
DUKE					
A+B	87 (41.0%)	103 (48.9%)	21 (10.1%)	277 (57.2%)	145 (42.8%)
C+D	67 (42.9%)	73 (46.8%)	16 (10.3%)	207 (58.0%)	105 (42.0%)
(χ^2/P)		0.148/0.929		0.040/0.842	
Tumor location					
Colon cancer	41 (40.0%)	60 (52.6%)	13 (11.4%)	142 (62.3%)	86 (37.7%)
Rectal cancer	109 (43.1%)	120 (47.4)	24 (9.50%)	338 (66.8%)	168 (33.2%)
(χ^2/P)		1.694/0.429		1.418/0.234	
Degree of differentiation					
Moderate/high differentiation	169 (46.2%)	164 (44.8%)	34 (9.0%)	502 (68.4%)	232 (31.6%)
Poor differentiation/undifferentiated	145 (39.5%)	167 (45.5%)	55 (15.0%)	457 (62.3%)	277 (37.7%)
(χ^2/P)		6.817/0.033		6.090/0.014	

of IGF-1 in patients with CRC. In the study, we demonstrated that people with the CT genotype might have a higher risk of CRC, compared with CC genotype carriers. Under dominant model, CT and TT genotype carriers might have a higher risk of CRC (*OR = 1.348 95% CI = 1.007-1.806 P = 0.045*). The frequency distribution of the T allele was significantly correlated with the degree of differentiation (P = 0.014). These findings may offer a new approach to screening for colorectal cancer. However, we did not observe any association between genotypes with disease stages, gender, and tumor location.

Previous research has proven that the IGF system includes two ligands and at least six IGF binding proteins that control the growth and development of the human body. When the level of IGF expression is abnormal or imbalanced, it may become a risk factor for cancer. There are several studies showed a direct correlation between colorectal cancer and IGF-1 accusing its involvement in the enhancement of cell proliferation, apoptosis, tumorigenesis, and vascular smooth muscle cell proliferation [11-14]. For instance, in a prospective nested case-control study by Palmqvist, including 260000 subjects, it was shown that individuals

with elevated circulating IGF-1 levels have an increased risk of colorectal cancer, which is consistent with our findings. Conditional logistic regression shows an increased risk of colon cancer as circulating IGF-1 levels increase (OR = 1.00, 1.89, 2.30, 2.66; P-trend = 0.03) [15]. However, they found that serum circulating IGF-1 concentration is not associated with rectal cancer. Key et al. conducted a meta-analysis including 17 prospective studies with a population of 4790 cases and 9428 matched controls. After adjusting for age, individuals with high levels of IGF-1 have an increased risk of breast cancer compared with patients with low-level IGF-1 (OR = 1.28 *95% CI 1.14-1.44 P<0.0001*) [16]. Given the above data, the importance of the IGF-1 in different types of cancers, including colorectal cancer and breast cancer, was shown.

The inter-individual variation of circulating plasma IGF-1 is determined to some extent by genetic factors and the environment [9]. Chen et al. revealed that there was strong linkage disequilibrium (LD) between rs35767, rs574-2612, and rs2288377, implying that the three SNPs may play an essential role in regulating IGF-1 levels [7]. In this study, one of the SNP polymorphisms in the promoter region of IGF-1 (rs35767) was studied. Jian et al. studied IGF-1 gene polymorphisms associated with diabetic retinopathy risk in Chinese Han population [17], and they observed that minor allele homozygote of rs35767 (TT) was obviously correlated with serum IGF-1 level, which is consistent with our findings. However, in the present study, we did not observe TT genotype carriers to have a higher risk of colorectal cancer compared with CC genotype carriers, under codominant model (*OR = 1.213 95 CI 0.734-2.005, P = 0.451*). In contrast, we observed a significant correlation between the presence of CT genotype of the promoter region of IGF-1 and the risk of colorectal cancer (*OR = 1.399 95% CI 1.029-1.901, P = 0.032*).

In the present study, the mean age for the case group was 65.8±9.5 years, with a higher incidence in males than females (59.7% and 40.3%, respectively) that matches the Chinese Cancer Society. However, we did not observe an association between genotypes of rs35767 and the risk of CRC after stratified according to gender. Our study confirmed finding by Ayman Yosry et al. [11] who studied 96 subjects of Egyptians, including 66 CRC patients and 30 healthy individuals. Ayman Yosry found that SNP rs35767 genotypes were not associated with colorectal cancer. However, the population included in Ayman Yosry's study was too small and may require large samples to verify the conclusions further.

In the present study, 367 patients, whose colorectal cancer stages, tumor location, and degree of differentiation had been determined by the oncologist, and then we assessed the association with rs35767 polymorphism genotypes. There was no association between colorectal cancer stages and genotype. However, we observed that the patients who carried T allele tend to have poor tissue differentiation. Therefore, the detection of related genes before surgery, it may help doctors to develop more reasonable surgical plans [18]. We also observed that subjects who had the C allele of SNP rs35767 are more frequent in rectal cancer, but there was no significance (P>0.05). Lu et al. demonstrated that overexpression of IGF-1 and IGF-1R mRNA in colorectal cancer is significantly higher than normal tissue and high-level IGF-1 is associated with the degree of tissue differentiation which is consistent with our findings [19]. However, in the study, we failed to demonstrate a higher association between the rs35767 polymorphic variants and tumor stage.

In our study, the level of LDL and TC were significantly higher in the case group than the healthy control group (*P<0.05*), which is consistent with the results of a Mendelian randomization study [20]. They have all proven that hyperlipidemia may be a risk factor for colorectal cancer. In another study conducted by Caihua [21], including 90 patients confirmed by histology, they demonstrated that LDL enhances intestinal inflammation and CRC progression via activation of reactive oxygen species (ROS) and signaling pathways including the MAPK pathway. Therefore, reduction of body weight and stains may be helpful in reducing CRC risk, and stains could also be evaluated as a potential adjunctive therapy for CRC [22].

Several limitations of our study should be noted. First, since the study subjects are of Chinese Han population, the results are most generalizable to the people of this ethnicity,

and it is not known whether our findings apply to other groups. Second, the statistical power for our current study is relatively low (40.0%), which may be due to the small sample size. Therefore, further studies involving larger populations and other ethnicities are needed. Third, environmental factors and other genetic factors were not considered in this study. Chen et al. proved that individual microsatellites or tag-SNPs might not be the primary regulatory elements of IGF-1 expression, and haplotypes have a better correlation with the concentration of circulating IGF-1 [9]. Therefore, other SNPs in the promoter region of IGF-1 should be considered in the future study, such rs22883-77 and rs5742612.

In conclusion, having at least one copy of the IGF-1 rs35767 gene (CT or TT genotypes) was associated with an increased risk of CRC, under the dominant model, and the patients who carried T allele of rs35767 tend to have poor tissue differentiation.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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