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Original Article

FTO gene polymorphisms and cholangiocarcinoma risk: a case-control study

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Abstract: It has been estimated FTO gene polymorphisms increase the risk of various cancers, while the correlation between polymorphisms of this gene and cholangiocarcinoma has not been reported. To investigate the relationship of FTO gene rs8050136, rs9939609 polymorphisms and the highly invasive carcinoma, the case-control study were designed. We collected the samples and clinical parameters of eligible patients and healthy controls, detected the genotypes of rs8050136 and rs9939609 by direct sequencing. Then correlations between different genotypes and the risk of cholangiocarcinoma were analyzed through SPSS 19.0 statistical software. However, the results provided no evidence to support the correlations: rs8050136 polymorphisms: A allele (OR=1.287, 95% CI=0.661~2.503, *P*=0.457), AC+AA genotype (univariate: OR=1.265, 95% CI=0.613~2.609, *P*=0.524; multivariate: AOR=1.177, 95% CI=0.517~2.682, *P*=0.697); rs9939609 polymorphism: A allele (OR=0.968, 95% CI=0.471~1.993, *P*=0.931), AT+AA genotype (univariate: OR=1.047, 95% CI=0.476~2.29, *P*=0.909). In sum, the FTO gene polymorphisms may have no evident correlation with the risk of cholangiocarcinoma in the Chinese.

Keywords: Cholangiocarcinoma, FTO gene, polymorphisms, case-control study

Introduction

Epidemiological statistics have show that the incidence and mortality rates for cholangiocarcinoma (CC) originating from biliary epithelial cells, have risen across the world, especially in the Western and Asian countries [1, 2]. The occurrence of cholangiocarcinoma is a multi-step process induced by many factors. The etiological factors differs geographically: in the Western world sclerosing cholangitis is the most common cause of morbidity, while in Asian countries, liver fluke disease and bile duct inflammation are defined as main causes [3-5]. Addionally viral hepatitis, obesity, diabetes, smoking, drinking, polymorphism and other factors also participate in the pathogenesis of cholangiocarcinoma [6, 7]. Compared to other digestive system neoplasms, cholangiocarcinoma is characterized by difficulty in early diagnosis, early metastasis, weak response to conventional treatments (such as radiotherapy, chemotherapy and surgical removal) and poor prognosis [8-10]. Thus screening risk factors, preventing occurrence of the disease and improving the diagnostic accuracy in early stage. have attracted attentions of researchers.

In recent years, obesity has become a common disease in worldwide, its incidence and mortality is increasing [5]. In many countries, obesity has become a major public health concern, which increases the risk of diseases relating to metabolism (including diabetes, hypertension, and coronary heart disease) and multiple tumors, such as breast cancer, thyroid cancer, colon cancer, prostate cancer, liver cancer and lymphoma [11]. It has been reported that insulin resistance, leptin, insulin-like growth factors, obesity-related inflammatory cytokines, the nuclear factor kappa beta system, and oxidative stresses are all possibly involved in the underlying biological and molecular mechanisms [12]. Many genes is associated with obesity, include fat mass and obesity associated gene, leptin, adiponectin, resistin. FTO (fat mass and obesity associated) most closely links to obesity, involves in fat metabolism, energy regulation, growth, strongly associated with many diseases and vaious neo-

plasms. FTO SNP has been demonstrated significantassociation with BMI, while the results are inconsistent in different studies. However, the relation between FTO SNPs and cholangiocarcinoma has not been reported.

Fat mass and obesity associated gene (FTO) located in chromosome 16q12.2 is closely related to obesity, encodes a 2-oxoglutarate (2-OG) Fe2-dependent dioxygenase, which acts as a DNA-demethylase, regulated diet and energy [13]. The FTO protein express in many tissues, such as mesenteric fat, adipose, pancreatic, liver, and hypothalamus [14]. Mutations in FTO that lead to a loss of function cause severe growth retardation, leanness and increased metabolic rate [15]. In recent years, some cohort and case-control studies have been conducted to estimate the relationship of FTO SNP and disease [16]. Multiple studies have found that FTO single nucleotide polymorphisms correlated with obesity, diabetes, coronary heart disease and cancer. FTO SNPs play various role in different tumors and in different populations [17, 18]. In the study we investigated the relationship between polymorphisms of FTO gene rs8050136 and rs9939609 and the onset risk.

Materials and methods

Study participants

In this study, 100 cholangiocarcinoma patients and 103 healthy controls were enrolled from Shandong provincial hospital and Taian central hospital. The purpose of this study was to define risk factors which contribute to the development of cholangiocarcinom. Cholangiocarcinoma patients eligible for the study were enrolled between January 1, 2006 and June 30, 2014. The cholangiocarcinoma patients were confirmed by certified histopathologists. Formalin-fixed paraffin-embedded tissues of cases were used to extract DNA. 103 healthy controls selected by age-and gender-matching to the cholangiocarcinoma patients. The patients and healthy controls had no history of any type of cancer at the time of recruitment. This study was approved by the Ethical committee of the two hospitals.

DNA isolation from cholangiocarcinoma cancers

In this study, use the black PREP FFPE DNA kit to isolate DNA of cholangiocarcinoma patients. The required thin (2 cm*10 μm) tissue sections on slides were dried at 37°C overnight. After soaking the tissue sections in 400 μl QPT solution and 25 μl protein kinase K in 50°C for 60 min, centrifugal separation was carried out in 15000 rpm for 1 m to carried out deparaffinization. To differentiate healthy from tumor tissue, the slide was stained with hematoxylin. The DNA was extracted using the black PREP FFPE DNA kit according to the manufacturer's instructions.

DNA isolation from peripheral venous blood of controls

Peripheral venous blood was obtained from each volunteer and promptly mixed with 300 μl natrium citricum and 600 μl TBP buffer solution after collection. Genomic DNA was extracted from EDTA 200 μl blood with the DNA isolation kit (Sangon Biotech, Inc, Shanghai China) according to the manufacturer's instructions. To obtain higher DNA concentrations, with some blood samples, lymphocyte separation was first performed according to the manufacturer's instructions (Sangon Biotech, Inc, Shanghai China). Briefly, 3 ml diluted blood samples were carefully centrifuged at 1,200×g for 20 min at RT, and lymphocytes from the interphase were washed twice in PBS. After that the DNA was isolated as above.

Genotyping of rs8050136 and rs9939609

The genotypes of rs8050136 and rs9939609 were assayed using direct sequencing. FTO polymorphism allele and genotype frequencies were measured, analyzed rs8050136, rs9939609 genotype and the risk of cholangiocarcinoma. The primers of the rs8050136 used were forward (5'-TTAACTAATTTCCGGTTTCCAT-3') and reverse (5'-GCTCTCGACATTTACACATTATCA-3'). rs9939609 the following primers: forward (5'-TGGCTCTTGAATGAAATAGGAT-3') and reverse (5'-CAGCTATTTGCATTTCAGTTTG-3'). Genotypes of rs8050136 and rs9939609 polymorphisms by sequencing.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 statistical software (SPSS Inc, Chicago, IL, USA) and data were presented as mean ± SD. Comparisons between two groups were performed by the independent t test or χ^2 analysis. Pearson's χ^2 test was performed to examine Hardy-Weinberg equilibrium of the case and control population. Univariate and multivariate logistic regression analysis was done

Table 1. Characteristics of the case-control study population

	Case (n=103)	Control (n=100)	*t* or χ^2	*P*
Age	60.64±11.01	59.29±10.42	-0.894	0.372
Sex			0.065	0.798
Male	68	58		
Female	35	42		
Smoke				
No	71	71	0.103	0.748
Yes	32	29		
Alcohol				
No	79	74	0.199	0.665
Yes	24	26		
Diabetes				
No	68	85	9.846	0.002
Yes	35	15		
Coron aryartery heart disease				
No	95	79	7.256	0.007
Yes	8	21		
Hypertension				
No	77	88	5.848	0.016
Yes	26	12		
Hyperlipidemia				
No	65	73	2.281	0.131
Yes	38	27		
Hbv				
No	102	97	1.081	0.298
Yes	1	3		

Table 2. Genotype distribution in Hardy-Weinberg equilibrium

Genotype			Predictive value (%)	Observed value (%)		
rs8050136		CC	83.72	84		
	Control	AC	15.55	15	χ^2=0.127	P=0.721
		AA	0.73	1		
		CC	79.8	80.58		
	Case	AC	19.1	17.48	χ^2=0.702	P=0.402
rs9939609		AA	1.1	1.94		
		TT	84.64	86		
	Control	AT	14.72	12	χ^2=3.414	P=0.064
		AA	0.64	2		
		TT	85.06	85.43		
	Case	AT	14.33	13.6	χ^2=0.261	P=0.609
		AA	0.61	0.97		

to determine the association of onset risk with gene polymorphisms. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. *P*<0.05 was considered statistically significant.

Results

Patients' characteristics

103 patients (68 males and 35 females) with the histopathological diagnosis of cholangiocarcinoma, and the mean age of patients was 60.64± 11.01 years. We recruited 100 healthy volunteers (58 males and 42 females) and mean age was 59.29±10.42. The cases and controls were age- and gender-matched using chi-square analysis, revealing *P* value of 0.372 and 0.798, as shown in **Table 1**. Cholangiocarcinoma group with history of diabetes, history of hypertension, history of coronary artery heart disease were higher than control group, gender, age, smoking, drinking, history of HBV and hyperlipidemia were similar (**Table 1**).

Hardy-weinberg equilibrium

Pearson's χ^2 test was performed to examine genotypic distribution of the case and control population. FTO rs8050136 and rs9939609 genotypic distributions were evaluated according to the Hardy-Weinberg equilibrium (**Table 2**).

FTO gene polymorphism and cholangiocarcinoma

rs8050136 polymorphisms and cholangiocarcinoma risk. Compared to control subjects, the genotype AC had no significant effect on the risk of cholangiocarcinoma (univariate: OR= 1.214, 95% CI=0.574-2.569, *P*=0.611; multi-

Table 3. Association of FTO rs8050136 polymorphisms and cholangiocarcinoma risk

Genotype	Group			Univariate			Multivariate		
	Case N (%)	Control N (%)		OR	95% CI	*P*	AOR	95% CI	*P*
CC	83 (80.58)	84 (84)		1			1		
AC	18 (17.48)	15 (15)	χ^2=0.567, *P*=0.753	1.214	0.574~2.569	0.611	1.105	0.465~2.626	0.82
AA	2 (1.94)	1 (1)		2.024	0.18~22.75	0.568	2.037	0.166~24.952	0.578
AC+AA	20 (19.42)	16 (16)		1.265	0.613~2.609	0.524	1.177	0.517~2.682	0.697
C	184 (89.32)	183 (91.5)	χ^2=0.556, *P*=0.456	1					
A	22 (10.68)	17 (8.5)		1.287	0.661~2.503	0.457			

Table 4. Association of FTO rs9939609 polymorphisms and cholangiocarcinoma risk

Genotype	Group			Univariate			Multivariate		
	Case N (%)	Control N (%)		OR	95% CI	*P*	AOR	95% CI	*P*
TT	88 (85.43)	86 (86)		1			1		
AT	14 (13.6)	12 (12)	χ^2=0.465, *P*=0.792	1.14	0.498~2.605	0.756	1.391	0.551~3.514	0.484
AA	1 (0.97)	2 (2)		0.489	0.043~5.488	0.562	0.438	0.034~ 5.667	0.528
AT+AA	15 (14.67)	14 (15.36)		1.047	0.476~2.29	0.909	1.218	0.507~2.925	0.659
T	190 (92.23)	184 (92)	χ^2=0.007, *P*=0931	1					
A	16 (7.77)	16 (8)		0.968	0.471~1.993	0.931			

variate: AOR=1.105, 95% CI=0.465~2.626, *P*=0.82); AC+AA genotype had no correlation with the risk of cholangiocarcinoma (univariate: OR=1.265, 95% CI=0.613~2.609, *P*=0.524; multivariate: AOR=1.177, 95% CI=0.517~2.682, *P*=0.697); A allele had no obvious correlation with the risk of cholangiocarcinoma (OR=1.287, 95% CI=0.661~2.503, *P*=0.457) (**Table 3**).

rs9939609 polymorphism and cholangiocarcinoma risk. The genotype AT had no significant association with the risk of cholangiocarcinoma (univariate: OR=1.14, 95% CI=0.498~2.605, *P*=0.756; multivariate: AOR=1.391, 95% CI=0.551~3.514, *P*=0.484); AT+AA genotype had no significant effect on the risk of cholangiocarcinoma (univariate: OR=1.047, 95% CI=0.476~2.29, *P*=0.909; multivariate: AOR=1.218, 95% CI=0.507~2.925, *P*=0.659); A allele had no significant effect on the risk of cholangiocarcinoma (OR=0.968, 95% CI=0.471~1.993, *P*=0.931) (**Table 4**).

Discussion

Cholangiocarcinoma has been widely recognized as an highly aggressive carcinoma with poor prognosis: the overall 5-year survival rate of the disease is less than 10% [19, 20]. Epidemiological data have demonstrated that obesity increase the risk of multiple tumors of the digestive system, including cholangiocarcinoma [21, 22]. FTO is one of the susceptibility genes of obesity, the FTO gene polymorphism has been linked with a variety of diseases by numerous etiological studies. While the the correlation between FTO gene polymorphism and the risk of cholangiocarcinoma has not been reports. This study described the distribution of different genotype of the FTO in cholangiocarcinoma patients and healthy controls, and investigate the relationship between the gene polymorphismand the risk of the disease by statistic analysis. However, the results did not support the correlation.

Obesity-related gene (FTO) plays pivotal roles in in energy homeostasis, adjustment of fat accumulation in the body, and participates in transcription regulation [23]. The ineffective function of the gene leads to growth retardation, increased metabolic rate and bulimia [24, 25]. The toe fusion mutant mice were found FTO gene deletion accompanied by severe developmental defects, including polydactyly, left-right asymmetry, hypothalamus developmental defects [26, 27]. FTO gene homozygous deficient mice can not survive in the embryonic period; In mice genetically engineered to lack FTO appeared postnatal growth retardation [28]. In humans, FTO mutation (R316Q) in patients with homozygous influences the growth and development of body, accompanys with symptoms of complex deformities [29].

The FTO SNP polymorphism has been linked to the risk of various disease. In 2007 FTO SNP polymorphism (rs9939609) were reported having significant association with overweight and obesity. And in 2009, for the first time, the relationship between Brennan FTO gene polymorphism and cancer risk in Central and Eastern Europe crowd was reported, FTO SNP rs9939609 A allele gene reduces the risk of lung cancer, while it could increase the risk of kidney cancer [30]. Subsequent studies found that FTO SNP polymorphism may increase the risk of some other tumors. So far, several cancer related SNP sites of FTO gene have been reported, including rs9939609, rs8050136, rs6499640, rs17817449, rs1477196, rs16953002, rs11075995 and rs1121980 [31].

We analyzed the relationship between FTO SNP and the risk of cholangiocarcinoma in the present study. In FTO rs8050136 sites, we categorized the genotypes into two: the CC genotype and the others (AC and AC+AA). The result showd similiar risk of the disease in the two groups. In rs9939609 locus, the object of the study were divided into those with TT genotype and the others with AT and AT+AA genotype. Compared with the TT genotype group, the other one was not demonstrated statistical difference in morbidity of cholangiocarcinoma. In short, our results indicated that there might be no significant correlation between the FTO SNP and the risk of cholangiocarcinoma. Over the past few years, reseachers have focused on discussing the role of the genotype rs8050136AA and rs9939609AA in different cancers, and got inconsistent conclusions. That may due to the unbalance geographical and ethnic distribution of the FTO SNP genotypes. In Asia, rs8050136-AA and rs9939609AA gene frequencies are much lower than the rate in the United States and the Europe [31, 32], which possibly leads to different relationship between the allele genotypes and the risk of various cancers.

In our study, rs8050136 A allele frequency (10.68%) in case group was higher than control group (8.5%), while the genotype frequency of rs9939609 A allele was similar in both case (7.77%) and control group (8%). Compared to studies of European and American countries, genotype frequencies of rs8050136 A allele and rs9939609 A allele were significantly lower.

According to data provided by NCBI, rs8050136 locus genotype AA and rs9939609 locus AA genotype frequecies in Asian population are lower than in Western countries [33, 34]. Frequency of FTO rs9939609 A allele in European populations is much higher than that in Asian population (35.5% vs 12-20%). FTO gene rs8050136 risk allele frequency in Asian population is about 17%, and the figure in Chinese Han population is 12%, also far below the European Caucasian population [33, 34]. In our study, rs8050136 A allele and rs9939609 A allele frequency were significantly lower than in European and American countries, which may be one of the reasons leading to the above negative results.

The role of BMI in FTO SNP induced cancer incidence is controversial in different studies. That could be explained by the fact the incidence of overweight and obesity is different in Western and Asian populations [35]. The relationship between FTO SNP and tumor staging has not been reported before. In addion, the correlation between the genotype of FTO and tumor differentiation has only been reported in a study, the result of which indicates that rs9939609A allele is a protective factor in prostate cancer of low degree differentiation [36]. This study has potential limitations. Restricted by the amount of samples, we did not provide enough data to analyze the relationship between BMI, FTO SNP and the risk of cholangiocarcinoma more objectively, either to discuss the effects of FTO variants on BMI more deeply. In further, Well-designed long-term study with larger amount of samples will be conducted to update the above data and analyze the association between FTO SNP and the staging and differentiation of cholangiocarcinoma.

Conclusion

In this study, the results showed that FTO gene polymorphisms were not correlated with the onset risk of cholangiocarcinoma, To further confirm this association, additional studies are warranted to elucidate the relationship between FTO SNP and the risk of cholangiocarcinoma.

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Disclosure of conflict of interest

None.

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