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Case-control study on IGFBP3 gene polymorphism and susceptibility to gastric cancer in a Chinese Han population

Huiwen Pan*; Guowen Ding; Jingfeng Zhu; Keping Chen

***Corresponding Author: Huiwen Pan**
School of Food and Biological Engineering, Jiangsu University, Zhenjiang, China.
Email: 2659947550@qq.com

Abstract

Background: This study investigated the role of the IGFBP3 gene rs3110697 and rs6953668 polymorphisms on the risk of gastric cancer.

Methods: A case-controlled study was conducted, including 490 primary gastric cancers and 1476 normal controls. The target gene fragment was amplified in blood samples using PCR. Genotyping was performed using the snapshot method.

Results: The control group had a consistent genotype frequency distribution and presented Hardy–Weinberg equilibrium. Smoking was correlated with the incidence of gastric cancer (P=0.001), and drinking history showed a significant difference between cases and controls (P<0.001). A significant difference was observed in the rs6953668 heterozygous mutations GA and GA+AA distribution frequencies between the case and control groups.

Conclusion: Smoking and drinking can increase the risk of gastric cancer. The IGFBP3 gene rs6953668 polymorphism was significantly correlated with the risk of gastric cancer. In contrast, the IGFBP3 gene rs3110697 polymorphism showed no significant correlation with the risk of gastric cancer.

Keywords

IGFBP3 gene; Gastric cancer; Single nucleotide polymorphism (SNP); rs6953668; rs3110697.

Abbreviations

GC: Gastric cancer; PCR: Polymerase chain reaction; OR: Odds ratio; MAF: Minor Allele Frequency; SNPs: Single nucleotide polymorphisms.

Introduction

According to 2020 statistics, over 1 million new cases of gastric cancer and about 769,000 deaths were recorded worldwide, ranking 5th in the incidence rate and 4th in the death rate among malignant tumors [1]. The incidence of gastric cancer is related to H. pylori infection and environmental factors, etc. Flow survey data showed that the incidence of gastric cancer varies significantly across different regions, with a higher incidence in East Asia. However, although the rate of Hp infection is high in Africa and South Asia, the incidence of gastric cancer is low. In addition, the rate of Hp infection in the Western population is 30%, but the final incidence of gastric cancer only reaches 0.1% to 1%. [2,3]. These data suggest that under the same environmental exposure, individuals with different genetic backgrounds have different susceptibility to gastric cancer. This susceptibility is currently thought to be determined by individual genetic factors, the most common of which are single nucleotide polymorphisms (SNPs), which are the main form of genetic variation between individuals [4].

SNPs can have an impact on tumor susceptibility [5,6]. Tumor formation is associated with cell proliferation, and regulatory genes in the cell proliferation pathway (Runx3, MDM2 and IGF) are highly likely to influence tumor development [7-9]. IGFBP-3 belongs to the Insulin-Like Growth Factor (IGF) family, which includes the peptide ligands IGF-I and IGF-II, insulin-like growth factor receptors and insulin growth factor binding proteins (IGFBP-1 to IGFBP-6, mainly IGFBP-3) [10]. IGFBP3 not only binds through IGF-I to regulate IGF-I levels, but also independently inhibits replication and promotes apoptosis [7]. Circulating levels of IGFBP-3 independently increase the risk of tumor development, including prostate, ovarian, breast, rectal and lung cancers [11]. Several case-control studies have focused on the association between IGFBP3 Single Nucleotide Polymorphisms (SNPs) and cancer risk. Terry et al. showed that IGFBP3 rs2270628 C>T was associated with an increased risk of ovarian cancer [12]. Breast cancer survival in Chinese women was significantly correlated with IGFBP3 rs3110697 G>A [13]. Furthermore, Chen et al. reported that IGFBP3 rs2270628 C>T and rs3110697 G>A single nucleotide polymorphisms were associated with a significantly increase risk of non-small cell lung cancer [14]. However, studies exploring the association between IGFBP3 gene polymorphisms and gastric cancer are scarce and the mechanism remains unclear. In order to explore their association, this paper examined two loci of IGFBP3 and assessed their association with the risk of gastric cancer, aiming to provide new methods for the prevention and treatment of gastric cancer.

Methods

Study population: 490 healthy subjects and 1476 GC patients were recruited from the Affiliated People's Hospital of Jiangsu University from May 2013 to June 2017. **Ethics statement:** This study was approved by the Ethics Committee of the Affiliated People's Hospital of Jiangsu University provided. Patients and controls provided written informed consent. **DNA extraction and genotype analysis:** Peripheral blood from each subject was used for DNA extraction. ExoI and FastAP were used to purify PCR amplicons and further analysis was conducted. ABI3730XL was used for sequence analysis to determine the genotypes with the Snapshot method, and the samples were analyzed with the Sample power software. The statistical power was set at 0.8, the Minor Allele Frequency (MAF) was set above 5%, and the two-sided

test with α= 0.05 as the significance level (Power and Sample Size Calculations, Version 3.0, January 2009). Multivariate and univariate analysis was performed to investigate the relationship between the IGFBP3 gene and patient characteristics. The factors included alcohol consumption, sex, smoking and age.

Table 1: Primary information for gene IGFBP3 gene rs3110697 and rs6953668 polymorphisms.

Genotyped SNPs	Gene(ID)	Chr.	Chr Pos (NCBI Build 38)	Region	MAFa for Chinese in database	MAF in our controls (n = 1,476)	*P*-value for HWEb test in our controls	Genotyping method	Genotyping value (%)
rs3110697	IGFBP3	7	45915430	Intron-variant	A=0.220	0.254	0.231	SNPscan	99.5%
rs6953668	IGFBP3	7	45916276	Intron-variant	A=0.081	0.047	0.867	SNPscan	99.3%

MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium

Table 2: Distribution of selected demographic variables and risk factors in gastric cancer cases and control.

Variate	Case (n=490) n(%)	Control (n=1,476) n(%)	*P*
Age (year)	60.65 ±11.43	61.30 ±9.60	0.220
			0.597
< 61	221(45.10)	686(46.48)	
≥61	269(54.90)	790(53.52)	
Sex			0.891
male	331(67.55)	1,002(67.89)	
female	159(32.45)	474(32.11)	
Smoking			**0.001**
No	309(63.06)	1,051(71.21)	
Yes	181(36.94)	425(28.79)	
Drinking			**<0.001**
No	374(76.33)	1,319(89.36)	
Yes	116(23.67)	157(10.64)	

Bold values indicate statistical significance (P < 0.05)

Statistical analysis

SPSS version 20.0 was used for data analysis (SPSS Inc., Chicago, IL, USA). The polymorphism frequency distributions were analyzed by the Chi-square test. The relationship between genotype frequencies and the risk of cancer was explored using logistic regression analysis and T-test analysis.

The findings indicated that IGFBP3 gene rs3110697 and rs6953668 polymorphisms were located on the first chromosome (Table 1). IGFBP3 gene rs3110697 and rs6953668 were located on chromosome 7, with rs3110697 chromosome position at 45915430, and rs6953668 chromosome position at 45916276. In the control group, the minor allele frequency (MAF) of rs3110697 was 0.254, while the minor allele frequency (MAF) of rs6953668 was 0.047. The controls demonstrated Hard Weinberg equilibrium values of 0.231 and 0.867 (P > 0.05). This implies that the sample population in this study was highly representative. More than 99.0% successful tests were obtained using the snapshot method.

Table 3: IGFBP3 gene rs3110697 and rs6953668 polymorphism in GC cases and controls and logistic regression analysis.

Genotype	GC Cases (n=490)		Controls (n=1,496)		Crude OR (95%CI)	*P*	Adjusted OR [a] (95%CI)	P_a
	n	%	n	%				
IGFBP3 rs3110697								
GG	254	52.37	827	56.18	1.00			
GA	201	41.44	541	36.75	1.21(0.98-1.50)	0.082	1.22(0.98-1.52)	0.080
AA	30	6.19	104	7.07	0.94(0.61-1.44)	0.775	0.95(0.76-1.18)	0.632
GA+AA	231	33.67	645	32.04	1.17(0.95-1.43)	0.143	1.07(0.97-1.19)	0.192
GA+GG	455	66.33	1368	67.96	1.15(0.76-1.76)	0.506	0.91(0.73-1.13)	0.390
IGFBP3 rs6953668 GA								
GG	452	93.39	1333	90.74	1.00			
GA	30	6.20	133	9.05	0.67(0.44-1.00)	0.050	0.62(0.41-0.95)	**0.027**
AA	2	0.41	3	0.21	1.97(0.33-11.80)	0.606	1.36(0.53-3.48)	0.518
GA+AA	32	6.61	136	9.26	0.69(0.47-1.04)	0.072	0.81(0.66-0.99)	**0.038**
GG+GA	482	9.37	1466	91.51	0.49(0.08-2.96)	0.603	1.38(0.54-3.81)	0.504

Bold values indicate statistical significance (P < 0.05)

The environmental risk factors and demographics of the study subjects are displayed in Table 2. There was no statistical difference in age and sex (P=0.597 and P=0.891, respectively) between the control and case groups. However, the case group showed a higher smoking rate than that of the controls (36.94% vs. 28.79%, P = 0.001), and a higher drinking rate than that of the controls (23.67% vs. 10.64%, P<0.001). This implies that smoking and drinking potentially increase the incidence of gastric cancer.

Analysis of the distribution of IGFBP3 rs6953668 GA showed no statistically significant difference in the distribution frequency of GA heterozygous mutations based on wild-type GG between the two groups (P = 0.050). The frequency distribution of rs6953668 GA in the case group was 6.2% and 9.05% in the control group. However, drinking, smoking, age and sex showed significant differences after adjustment using logistic regression (Pa = 0.027). The distribution frequency of GA+AA mutants in the two groups was P =0.072, the frequency distribution of rs6953668 GA+AA in the case group was 6.61% and 9.26% in the control group, and after adjustment of confounding factors was statistically difference Pa = 0.038,OR 95%CI=0.81(0.66-0.99) (Table 3).

The findings showed no significant difference in the IGFBP3 rs3110697 frequency distribution between the case group and the healthy group in all types. With wild-type GG as reference, no significant difference was observed in the distribution frequency of GA, AA, GA+AA, and GA+GG mutations between the case group and the control group (P = 0.082, Pa= 0.080; P = 0.775, Pa= 0.632; P = 0.143, Pa= 0.192; P = 0.506, Pa= 0.390, respectively).

Table 4 displays the stratified IGFBP3 gene rs6953668 polymorphism. Wild-type GG was used as the reference genotype, GA indicates the wild type genotype, and AA represents the homozygous genotype. In the gender subgroup, heterozygous GA mutations in the male group showed statistically significant dif-

Table 4: Stratified analyses between IGFBP3 gene rs6953668 polymorphism and risk by sex, age, smoking status and alcohol consumption.

Variate	IGFBP3 rs6953668 (Case/control)			OR(95%CI);*P*				
	GG	GA	AA	GG	GA	AA	GA+AA	AAvs(GA+GG)
Sex								
Male	308/ 903	18/90	1/3	1.00	0.59(0.35-0.99)	0.98(0.10-9.43)	0.59(0.36-0.99)	1.02(0.10-9.80)
					***P*:0.043**	*P*:0.984	***P*:0.047**	*P*:0.989
Female	144/ 430	12/43	1/0	1.00	1.20(0.62-2.34)	0.25(0.22-0.29)	1.11(0.58-2.12)	4.03(3.52-4.62)
					P:0.592	*P*:0.252	*P*:0.757	*P*:0.082
Age (years)								
< 61	200/ 620	17/ 61	1/1	1.00	0.86(0.49-1.51)	3.1(0.19-48.79)	0.90(0.52-1.56)	3.14(0.20-50.38)
					P:0.609	*P*:0.400	*P*:0.706	*P*:0.394
≥61	252/713	13/72	1/2	1.00	0.51(0.28-0.94)	1.42(0.13-15.67)	0.535(0.30-0.97)	1.481(0.13-16.4)
					***P*:0.028**	*P*:0.776	***P*:0.035**	*P*:0.747
Smoking status								
Never	285/ 949	18/98	2/0	1.00	0.61(0.36-1.03)	0.99(0.98-1.00)	0.68(0.41-1.12)	0.99(0.98-1.00)
					P:0.061	*P*:0.054	*P*:0.127	*P*:0.051
Ever	167/384	12/35	0/3	1.00	0.79(0.40-1.56)	1.01(0.33-1.02)	0.73(0.37-1.43)	1.01(0.99-1.02)
					P:0.492	*P*:0557	*P*:0.350	*P*:0.558
Alcohol use								
Never	349/1193	20/118	1/2	1.00	0.58(0.36-0.95)	1.71(0.16-18.91)	0.60(0.37-0.97)	1.78(0.16-19.65)
					***P*:0.027**	*P*:0.538	***P*:0.034**	*P*:0.525
Ever	103/140	10/15	1/1	1.00	0.91(0.39-2.10)	1.36(0.08-21.99)	0.93(0.42-2.10)	1.37(0.09-22.16)
					P:0.818	*P*:0.828	*P*:0.870	*P*:0.823

Bold values indicate statistical significance (P < 0.05)

ferences between the cases and the control group, P=0.043 and OR 95%CI=0.59(0.35-0.99). In addition, heterozygous GA+AA mutations in the male group also showed statistically significant differences between the cases and the control group, with P=0.047 and OR 95%CI=0.59(0.36-0.99). However, no statistical difference was found in other genotypes.

In the age subgroup, heterozygous GA mutations in the ≥61 group revealed statistically significant differences between the cases and the control group, with P=0.028 and OR 95%CI=0.51(0.28-0.94). Furthermore, heterozygous GA+AA mutations in the ≥61 group also showed statistically significant differences between the cases and the control group, with P=0.035 and OR 95%CI=0.535(0.30-0.97).

In the alcohol use subgroup, heterozygous GA mutations and heterozygous GA+AA mutations in the "never" alcohol use subgroup showed statistically significant differences between the cases and the control group, with P=0.027 and OR 95%CI=0.58(0.36-0.95), and P=0.034 and OR 95%CI=0.60(0.37-0.97), respectively. Table 5 Rs3110697 polymorphism in IGFBP3 gene according to stratification results: wild-type GG represents the reference genotype, GA indicates wild type genotype, AA represents the homozygous genotype, dominant model, and recessive model, with no statistical significance in each group.

Table 5: Stratified analyses between IGFBP3 gene rs3110697 polymorphism and risk by sex, age, smoking status and alcohol consumption.

Variate	IGFBP3 rs3110697 (case/control)	OR(95%CI); *P*				
	GG GA AA	GG	GA	AA	GA+AA	AAvs(GA+GG)
Sex						
Male	175/ 566 130/363 22/69	1.00	1.14(0.88-1.48)	1.01(0.61-1.69)	1.12(0.87-1.47)	0.97(0.59-1.60)
			P:0.335	*P*:0.960	*P*:0.384	*P*:0.908
Female	79/261 71 /178 8/35	1.00	1.32(0.91-1.91)	0.76(0.38-1.70)	1.23(0.85-1.76)	0.67(0.30-1.47)
			P:0.146	*P*:0.495	*P*:0.269	*P*:0.316
Age (years)						
< 61	113/ 381 91/ 251 16/51	1.00	1.22(0.89-1.68)	1.06(0.58-1.93)	1.20(0.88-1.62)	0.97(0.54-1.74)
			P:0.217	*P*:0.854	*P*:0.252	*P*:0.924
≥61	141/446 110/290 14 /53	1.00	1.20(0.90-1.60)	0.84(0.45-1.55)	1.14(0.87-1.51)	1.29(0.70-2.37)
			P:0.218	*P*:0.569	*P*:0.347	*P*:0.408
Smoking status						
Never	157/ 587 128/391 22/71	1.00	1.22(0.94-1.60)	0.86(0.52-1.44)	1.20(0.93-1.55)	1.06(0.45-1.75)
			P:0.136	*P*:0.571	*P*:0.166	*P*:0.808
Ever	97/ 240 73 /150 8/33	1.00	1.20(0.84-1.74)	0.60(0.27-1.35)	1.10(0.77-1.56)	0.56(0.25-1.23)
			P:0.319	*P*:0.211	*P*:0.613	*P*:0.142
Alcohol use						
Never	195/743 153/483 22/90	1.00	1.21(0.95-1.54)	0.93(0.57-1.52)	1.16(0.92-1.47)	0.86(0.53-1.39)
			P:0.125	*P*:0.777	*P*:0.199	*P*:0.542
Ever	59/84 48/58 8/14	1.00	1.18(0.71-1.96)	0.81(0.32-2.06)	1.11(0.68-1.79)	0.76(0.31-1.87)
			P:0.526	*P*:0.663	*P*:0.679	*P*:0.548

Discussion

Probably related to diet, H. pylori infection, inflammation, genetic factors and environmental factors, etc. Genetic factors play an important role in the development of gastric cancer, but the underlying mechanism remains unclear [15,16]. IGFBP-3 is a major type of IGF-binding protein with a relatively conserved structure and a high affinity for IGF-1. Based on previous studies, it is believed to be a multifunctional protein that inhibits the growth of cancer cells and induces apoptosis [17,18]. IGFBP3 inhibits the proliferation and induces apoptosis in a variety of tumor cells, including prostate, colorectal and gastric cancers, by interfering with the activity of IGF-I [19-21].

There are numerous studies related to gastric cancer and genetic polymorphisms. For example, SEMA5A, a gastric cancer-associated gene, is highly expressed in gastric cancer cells and promotes the proliferation and metastatic biological activity of cancer cells [22]. Zhao et al. found that TLR2 rs3804100 was associated with gastric cancer prognosis and was independent of Helicobacter pylori infection [23]. Furthermore, Emmanouil Liarmakopoulos et al. discovered that the E-select in S128R C allele might confer increased susceptibility to gastric cancer development and was correlated with a poor prognosis [24]. Nevertheless, there are few studies exploring the gene polymorphisms associated with IGFBP3 and gastric

cancer.

In this study, the rs6953668, and rs3110697 locus polymorphisms of the IGFBP3 gene were detected in gastric cancer patients and healthy individuals. The genotype frequency distribution of these two loci met the criteria of Hardy-Weinberg equilibrium law, and the samples were representative of the population. Wild-type GG-based GA heterozygous mutations demonstrated no statistically significant difference between the two groups (P=0.050). However, after adjustment using logistic regression, significant differences between the groups were found in drinking, smoking, age and sex (Pa = 0.027). The frequency of distribution of GA+AA mutants in both groups was P=0.072, statistically different after adjusting for confounding factors Pa=0.038, OR 95% CI=0.81 (0.66-0.99). This finding is consistent with Tang et al., who reported that the IGFBP3 gene rs6953668 G > A polymorphism may be associated with genetic susceptibility to EGJA in the Han Chinese population in eastern China [25]. In further stratification experiments, the mutant phenotype of IGFBP3 gene rs6953668 at this locus showed significant differences in sex, age and alcohol consumption. Age 61 years or older, male, and the presence or absence of alcohol consumption were all factors affecting the association of gastric cancer with this gene polymorphism.

In this study, no statistically significant allele frequencies were observed at the rs3110697 locus of the IGFBP3 gene between GC patients and healthy subjects. There were no significant differences in the gene model and variant distribution in GC patients compared to controls. In addition, analysis of age, alcohol consumption, smoking, and gender for different genotypes in the case group rs3110697 showed no significant correlation with gastric cancer susceptibility. This is consistent with Khatoon Karimi et al., who found that IGFBP3 rs3110697 was not associated with the risk of colorectal cancer [26]. However, Liu et al. found that IGFBP3 rs3110697 G>A was associated with a significantly reduced risk of ESCC [27]. The difference in findings may be due to the size of the sample, and differences between diseases and races, among others.

However, this study also has some limitations. First, a limited number of patients with gastric cancer were included, which may prevent strong conclusions from being drawn. Second, only 2 SNPs were selected and genotyped, which may lead to insufficient coverage. Based on the complexity of gastric cancer disease and many uncertainties, a larger sample size and multi-gene combination analysis should be performed to confirm the results.

In conclusion, this study suggests that the IGFBP3 gene rs6953668 G>A polymorphism may be associated with genetic susceptibility to gastric cancer in the Chinese Han population. In contrast, the IGFBP3 gene rs3110697 polymorphism may not be associated with genetic susceptibility to gastric cancer.

Conclusions

Smoking and drinking are associated with the occurrence of gastric cancer. IGFBP3 gene rs6953668 polymorphism is significantly associated with susceptibility of GC.

Declarations

Supplementary Information: The data used to support the findings of this study are included within the supplementary information file.

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Authors' contributions : LZQ made substantial contributions to the conception, design, conduct, data acquisition. PHW,FZJ ,SAZ interpreted the clinical trial, selected samples, directed experiments, data analysis, and interpretation, and performed data acquisition and analysis; PHW and FZJ wrote and edited the manuscript. All authors agreed both to be personally accountable for the author's own contributions and ensure that questions related to accuracy or integrity of any part of the work. All authors read and approved the final manuscript.

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Availability of data and materials : The data that support the funding of the present are included in the supplementary information file named supplementary dates.

Ethics approval and consent to participate : This study has been approved by The Ethics Review Committee of the Affiliated People's Hospital of Jiangsu University. The principles of the Declaration of Helsinki were followed when conducting the study. The subjects had agreed and provided written informed consent.

Consent for publication : Not applicable.

Competing interests : Not applicable.

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Authors Information: Huiwen Pan[1]*; Guowen Ding[1]; Jingfeng Zhu[1]; Keping Chen[2]
[1]Cardiothoracic Surgery Department, the Affiliated People's Hospital of Jiangsu University, Jiangsu, China.
[2]Department of Otolaryngology, the Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou, Jiangsu, China.

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