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CLEC3A gene three polymorphisms and risk of gastric cancer in Northwestern Chinese population

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Abstract: This study aimed to evaluate the association between the CLEC3A gene polymorphisms (rs2735401/rs2293776/rs2072665) and the gastric cancer risk in the Northwestern Chinese population. A hospital-based case-control study was conducted on 681 cases and 756 healthy controls. Odds ratio (OR) and 95% confidence intervals (CI) were applied to evaluate the association of the CLEC3A polymorphisms on gastric cancer risk. We found that there was no significant association between the CLEC3A polymorphisms and gastric cancer susceptibility, which was detected in the main analysis or stratification analyses of age, gender, and clinical stages. Our findings verified that the CLEC3A polymorphisms are not associated with gastric cancer susceptibility in the Northwestern Chinese population; other polymorphisms should be investigated to further clarify the susceptibility to gastric cancer.

Introduction

Gastric cancer (GC) is one of the most prevalent cancers worldwide and the third major cause of cancer mortality (Bray *et al.*, 2018; Gjyshi *et al.*, 2018). In China, it is the second leading cause of cancer death among both men and women, with approximately 679,100 new cancer cases and 498,000 cancer deaths reported in 2015 (Chen *et al.*, 2016). Although there have been advances in the treatment strategies for gastric cancer, the prognosis of gastric cancer is still poor, the 5-year survival rate is only 20–30% because most cases are diagnosed in an advanced stage (Tahara *et al.*, 2010). GC development is influenced by individual genetic susceptibility, environmental components (Maccormick *et al.*, 2019), and/or dietary habits (Hartgrink *et al.*, 2009). Genetic factors have been found to play an important role in the development of gastric cancer (Baroudi and Benammar-Elgaaied, 2016). To clarify the genetic background of gastric cancer, it is necessary to identify the genetic factors specifically such as single nucleotide polymorphisms (SNP), and the relationship between SNP and gastric cancer has been studied. A study found that the ERCC1, XPG, and mTORC1 Gene may affect the risk of gastric cancer in the Chinese Han population (He *et al.*, 2012; He *et al.*, 2013; He *et al.*, 2018), but no positive association was found between the three LIG3 (DNA ligase III) SNPs and gastric cancer risk in single-locus analysis or combined risk genotypes analysis (Hua *et al.*, 2019).

C-type lectin domain family 3 member A (CLEC3A, originally called CLECSF1) was first described as a cartilage-derived member of the C-type lectin superfamily and according to its domain structure assigned to the tetranectin IX group, together with tetranectin (CLEC3B) and stem cell growth factor (SCGF) with α and β forms (CLEC11A) (Neame *et al.*, 1999). The C-type lectins form a diverse protein family with many different functions across species. Most members are found extracellularly and carry C-type carbohydrate recognition domains (CRD) that, in some cases, specifically recognize or bind proteins, lipids, or carbohydrates in a Ca^{2+} dependent manner; whereas, those in other proteins only form a structural motif. Human *CLEC3A* mRNA has been detected in normal breast and breast cancer tissue as well as in two colon cancer cell lines, and *CLEC3A* associates with cell adhesion (Tsunezumi *et al.*, 2009). Cell adhesion influenced results in tumor cell proliferation and metastasis (Boguslawska *et al.*, 2018). In terms of tumor tissue, *CLEC3A* expression was markedly higher in breast invasive ductal cancer tissues than normal breast tissues or adjacent normal tissue (Ni *et al.*, 2018). It is suggested that *CLEC3A* may be related to the development of breast cancer. Additionally, *CLEC3A* was reported to activate the plasminogen activation via enhancing tissue plasminogen activator (Lau *et al.*, 2018). It was found that the plasminogen activator system was identified as one of

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the major mechanisms involved in the processes of cell invasion and metastatic spreading (Duffy *et al.*, 2014; Resmini *et al.*, 2017).

The *CLEC3A* gene coding the CLEC3A protein also resides in the fine-mapped region on chromosome 16q23 (Rezaee *et al.*, 2006). The murine and human *CLEC3A* gene consists of three exons. The first exon codes for a potential signal peptide with 22 amino acids and the subsequent 16 amino acids. The second exon encodes 27 amino acids and the third a CRD domain of 130 amino acids (Neame *et al.*, 1999). In human colon carcinoma cells, CLEC3A is a membrane-associated substrate for matrix metalloproteinase-7 (MMP-7), and has been speculated that cleavage of CLEC3A by MMP-7 in the tumor microenvironment may affect tumor cell invasion and metastasis by modulating cell adhesion and the plasminogen/plasminogen-activator system (Tsunezumi *et al.*, 2009). In a proteomic analysis of high-density lipoprotein (HDL), CLEC3A was identified as an HDL-associated protein (Rezaee *et al.*, 2006). However, the relationship between CLEC3A polymorphisms and tumors has not been studied.

Therefore, in this study, we analyzed the relationship between the *CELC3A* gene three polymorphisms (rs2735401 T>G/rs2293776 C>G/rs2072665 T>C) and GC susceptibility in a cohort of GC and healthy controls in the Northwestern Chinese population.

Materials and Methods

Ethics

This study was approved by the Ethics Committee of The Air Force Medical University. The procedures were performed according to the approved guidelines and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The signed informed consent was obtained from each participant included in the study.

Study subjects

A total of 681 GC patients and 756 healthy control subjects from Chinese genetically unrelated Northwestern people were enrolled in the study, including subjects from two hospitals in Xijing and Tangdu hospital in Shaanxi province. All patients were diagnosed as having GC based on a histopathological examination. None of the patients had a history of any other tumors. The control subjects were randomly chosen among people living in Shaanxi province, with match age and sex.

Sample collection and genotyping

Peripheral venous blood samples (5 mL) were collected from all subjects in EDTA vacutainers. Genomic DNA was obtained from the peripheral blood lymphocytes of study subjects using the Genomic DNA Extraction Kit (Omega Bio-Tek, Norcross, GA, USA or GoldMag Ltd, Xian, China) according to the manufacturer's protocol. Agena Mass ARRAYAssay Design 4.0 software was used to design the multiplexed SNP Mass EXTEND assay. The CLEC3A polymorphisms were genotyped on the Agena Mass ARRAY RS1000 platform according to the standard protocol (Applied Biosystems, Foster City, CA, USA). Then, Agena Typer 4.0 software was applied to analyze and manage our data. Quality control was performed with eight negative control and positive control samples in each 384-well plate. In addition, 10% of the samples were randomly selected for a second genotyping for validation of the assay, and the concordance rate was 100%.

Statistical analysis

We used SPSS version 19.0 software (SPSS, Chicago, IL) and Microsoft Excel (Redmond, WA) to analyze all the related data. A value of $p < 0.05$ was considered statistically significant. Pearson's $\chi 2$-test was used to detect differences in demographic variables, risk factors distribution, and *CLEC3A* genotypes distribution between the case and control groups. Frequencies of the variants were estimated using the Hardy–Weinberg equilibrium (HWE) (p-value calculated by the exact test) to compare the expected frequencies of the genotypes in the control groups. PLINK software was used to calculate the odds ratios (OR) and 95% confidence intervals (CI) by unconditional logistic regression analysis with adjustment for age and gender (Jin *et al.*, 2015). Finally, we measured the linkage disequilibrium (LD) between loci, haplotype construction, and the genetic association was calculated by unconditional logistic regression. The Haploview was used to construct haplotype and genetic association at significant polymorphism loci and to estimate the pairwise LD, haplotype software (version 4.2) (Guruvaiah *et al.*, 2014).

Results

Characteristics of the study population

Overall, the selected variables were significantly different between GC patients and controls regarding the distribution of age and gender ($p < 0.001$ and $p < 0.001$, respectively). The distributions of age, gender, and clinical stages of the study subjects are summarized in Tab. 1. The mean age was 57.57 ± 10.83 years for GC patients and 52.58 ± 8.71 years for the controls. Males were predominant in both the GC and control groups. The proportion of male subjects was significantly higher in the group with GC (77.4%), whereas the number of female subjects was higher in the control group (35.3%). Most of the patients had stage II disease, followed by stage III, stage I, and stage IV. Tumors less than 5 cm in diameter accounted for more than half of the case group.

Association of the three CLEC3A polymorphisms with the risk of GC

The genotype distributions of the CLEC3A polymorphisms in GC patients and controls are summarized in Tab. 2. Compared with rs2735401 TT homozygote, the frequencies of rs2735401 GT and GG genotypes in GC cases and controls did not show significant difference ($p = 0.148$ and $p = 0.454$). The OR after adjustment of risk factors (age and sex) were 1.04 (95%CI = 0.83–1.31, $p = 0.145$) for GT and 0.83 (95% CI = 0.58–1.21, $p = 0.520$) for GG genotypes. Individuals with variant genotypes (GT + GG) had a 0.99-fold reduce in risk of GC but had no significant difference from TT genotype (adjusted OR = 0.99, 95%CI = 0.80–1.24, $p = 0.96$).

Compared with rs2293776 CC homozygote, the frequencies of rs2293776 CG and GG genotypes in GC cases

TABLE 1

Characteristics and clinical features of the gastric cancer (GC) cases and the control group

Variables	GC (N = 681)	Controls (N = 756)	p^a
Age (years), (Mean ± SD)	57.57 ± 10.83	52.58 ± 8.71	<0.001
<55	251 (36.86)	429 (56.75)	
>55	430 (63.14)	327 (43.25)	
Gender			
Male, N (%)	527 (77.4)	489 (64.7)	<0.001
Female, N (%)	154 (22.6)	267 (35.3)	
Clinical stage			
I	126 (18.50)		
II	316 (46.40)		
III	148 (21.73)		
IV	55 (8.08)		
NA	36 (5.29)		
Tumor diameter (cm)			
<5	375 (55.07)		
≥5	272 (39.94)		
NA	34 (4.99)		
Recurrence/metastasis			
Negative	377 (55.36)		
Positive	287 (42.14)		
NA	17 (2.50)		

Note: GC, gastric cancer; N, number of patients; SD, standard deviation; NA, not applicable; p^a, p value based on a two-sided χ^2 test for distributions between GC cases and control group.

and controls also had no significant difference ($p = 0.163$ and $p = 0.339$, respectively). The adjusted OR were 0.98 (95%CI = 0.78–1.25, $p = 0.075$) for CG group and 0.90 (95%CI = 0.55–1.46, $p = 0.863$) for GG group. Individuals with variant genotypes (CG + GG) had only a 0.97-fold risk of GC but with no difference compared with CC homozygote carriers (adjusted OR = 0.97, 95%CI = 0.77–1.22, $p = 0.79$).

Compared with rs2072665 TT homozygote, the frequencies of rs2072665 TC and CC genotypes in GC cases and controls had no significant difference ($p = 0.48$ and $p = 0.37$, respectively). The adjusted OR were 1.14 (95%CI = 0.88–1.48, $p = 0.33$) for TC group and 1.24 (95%CI = 0.91–1.70, $p = 0.37$) for CC group. Individuals with variant genotypes (TC + CC) had a 1.17-fold risk of GC but with no difference compared with CC homozygote carriers (adjusted OR = 1.17, 95%CI = 0.92–1.50, $p = 0.20$).

In summary, there was no significant association observed between the *CLEC3A* polymorphisms and GC susceptibility in any comparison (Tab. 2).

Stratification analysis of the CLEC3A polymorphisms and GC risk

Because age and gender are reported to be the two major risk factors of gastric cancer, and this disease is reported to be more common in men over the age of 55 than in other groups (Billington, 1960; Christie *et al.*, 1997; Silecchia *et al.*, 2005). We further explored the association between the polymorphisms and GC risk in analyses stratified by age, gender, and clinical stages (Tab. 3). We found that regardless of *CLEC3A* rs2735401 T > G, rs2293776 C > G, or rs2072665 T > C, no significant associations were observed in older than 55 years or in those 55 years or younger. In addition, the three polymorphisms were not significantly associated with GC risk in either females or males. Finally, CG/GG genotypes were not associated with GC risk in patients at Stages I + II or Stages III + IV.

Discussion

In this first hospital-based case-control study, we investigated the association of the *CLEC3A* polymorphisms with the risk of gastric cancer in 681 patients and 756 healthy controls of Northwestern Chinese origin. We found that the *CLEC3A* genotypes not significantly increased the risk of gastric cancer in the Northwestern Chinese population. Overall, this study of its kind indicates that the *CLEC3A* gene polymorphisms may not be associated with GC susceptibility in the Northwestern Chinese population.

The incidence rate of GC ranks fifth, and its mortality remains third among all human cancers in both sexes in 2018 (Bray *et al.*, 2018). The development of gastric cancer represents a complex interaction of infectious agents with environmental and host factors (Rawla and Barsouk, 2019; De Re *et al.*, 2019). As surgical techniques improve and progress is made in traditional radiotherapy, chemotherapy, and the implementation of neoadjuvant therapy, the 5-year survival rate of early gastric cancer can reach >95%

TABLE 2

Association between *CLEC3A* rs2735401 T > G, rs2293776 C > G, and rs2072665 T > C polymorphisms and gastric cancer (GC) susceptibility

Genotype	Control		GC		OR (95% CI)	p^a	OR (95% CI)	p^b
	n	%	n	%				
rs2735401								
TT	364	48.1	326	47.9	1.00		1.00	
GT	306	40.5	287	42.2	1.05 (0.84–1.30)	0.77	1.04 (0.83–1.31)	0.96
GG	86	11.4	67	9.8	0.87 (0.61–1.24)	0.59	0.83 (0.58–1.21)	0.51
GT + GG	392	51.9	354	52.1	1.01 (0.82–1.24)	0.94	0.99 (0.80–1.24)	0.96
TT + GT	670	88.6	613	90.2	1.00		1.00	
GG	86	11.4	67	9.8	0.85 (0.61–1.19)	0.35	0.82 (0.58–1.17)	0.27
rs2293776								
CC	480	63.4	432	63.3	1.00		1.00	
CG	234	30.9	216	31.7	1.03 (0.82–1.29)	0.91	0.98 (0.78–1.25)	0.93
GG	43	5.7	34	5	0.88 (0.55–1.40)	0.82	0.90 (0.55–1.46)	0.9
CG+GG	277	36.6	250	36.7	1.00 (0.81–1.24)	0.98	0.97 (0.77–1.22)	0.79
CC+CG	714	94.3	648	95	1.00		1.00	
GG	43	5.7	34	5	0.87 (0.55–1.38)	0.56	0.90 (0.55–1.46)	0.67
rs2072665								
TT	215	28.4	176	26	1.00		1.00	
TC	382	50.5	346	51.1	1.11 (0.86–1.42)	0.76	1.14 (0.88–1.48)	0.48
CC	159	21	155	22.9	1.19 (0.88–1.60)	0.5	1.24 (0.91–1.70)	0.37
TC + CC	541	71.6	501	74	1.13 (0.90–1.43)	0.3	1.17 (0.92–1.50)	0.20
TT + TC	597	79	522	77.1	1.00		1.00	
CC	159	21	155	22.9	1.11 (0.87–1.43)	0.39	1.14 (0.88–1.48)	0.33

Note: GC, gastric cancer; OR, odds ratio; CI, confidence interval; p^a, *p* value based on a $\chi 2$ test for genotype distributions between GC and control group; p^b, *p* value after adjusted for age and gender.

TABLE 3

Stratification analyses for the association between *CLEC3A* polymorphisms and gastric cancer (GC) susceptibility

Variables	CC	CG/GG	Crude OR	*p*	Adjusted OR	p^a
	(GC/Controls) (95% CI)				(95% CI)	
Age, years						
<55	153/274	97/156	1.11 (0.81–1.54)	0.51	1.12 (0.81–1.54)	0.50
≥55	277/206	153/121	0.94 (0.70–1.27)	0.69	0.79 (0.56–1.10)	0.16
Gender						
Females	101/179	53/88	1.07 (0.70–1.62)	0.76	1.01 (0.66–1.55)	0.95
Males	330/300	197/189	0.95 (0.74–1.22)	0.68	0.89 (0.67–1.18)	0.41
Clinical stages						
I + II	277	148	1.05 (0.81–1.23)	0.52	1.07 (0.80–1.23)	0.60
III + IV	163	93	0.86 (0.79–1.09)	0.63	0.91 (0.83–1.11)	0.56

Note: GC, gastric cancer; OR, odds ratio; CI, confidence interval; *p*, *p* value before adjusted for age and gender; p^a, *p* value after adjusted for age and gender, omitting the corresponding stratification factor.

(Song *et al.*, 2017). However, the low rate of early diagnosis means that most patients have advanced-stage disease at diagnosis and so the best surgical window is missed, and the 5-year survival rate is low (Wu *et al.*, 2015).

SNPs are the most common type of genetic variation, which makes them excellent biological markers. On the other hand, SNPs, including those that fall within the coding or noncoding regions of genes, may affect the gene

transcription and translation, as well as the structure and function of proteins, contributing to changing the host susceptibility to diseases (Liang *et al*., 2019). At present, studies indicate that gene polymorphisms were closely related to the susceptibility of gastric cancer, including *XPG* (Wang *et al*., 2019), *MUC4* (Nabatchian *et al*., 2019), cyclooxygenase-2 (Chen *et al*., 2019), *PSCA* (Yan *et al*., 2019) and so on.

The C-type lectin domain family is classified into 17 subgroups, but the classification criteria are not consistent with regard to function, phylogenesis criteria, or gene structure (Zelensky and Gready, 2005). *CLEC3A* is a poorly characterized protein belonging to the superfamily of C-type lectins (Lau *et al*., 2018), and associated with an increased risk of a variety of multiple diseases (Karlsson *et al*., 2010; Elezagic *et al*., 2019; Wilson *et al*., 2016).

Previously, we have found no association of *CLEC3A* gene expression between cancer and normal tissue samples via immunohistochemical analysis (data not published). Therefore, we ought to explore the role of the *CLEC3A* polymorphisms via genetic analysis of patient samples. Since there are limited reports illustrating the *CLEC3A* polymorphisms rs2735401, rs2293776, and rs2072665 in cancer progression while regulating coagulation, we chose to analyze these polymorphisms in GC patient (Lau *et al*., 2018; Hua *et al*., 2019). In the present study, we genotyped 681 GC patients and 576 cancer-free controls from two different hospitals to evaluate the association between the *CLEC3A* gene polymorphisms and GC susceptibility. We found that the *CLEC3A* gene three polymorphisms were no significant association and GC susceptibility in any comparison. Moreover, although reports showed that age and gender are the two major risk factors of gastric cancer (Lu *et al*., 2012), our stratified analysis by age and gender did not modify the association between the three polymorphisms and the risk of gastric cancer, similar results were found in clinical stages.

Although our overall results suggest no association, it is important to consider that GC is a multifactorial disease resulting from multiplicative interactions between environmental factors and genetic backgrounds. Thus, a main limitation of this study is the lack of available information on some valuable parameters such as parental exposure, dietary intake, and living environment. Selection bias is another obvious potentially confounding factor, as the study population certainly is not representative of the whole Chinese population.

CLEC3A has been investigated in a few studies, limiting our discussion since we cannot compare our results with other ethnic groups. Thus, to better elucidate the role of the *CLEC3A* polymorphisms with GC susceptibility, future studies should as many as possible.

Our study represents the first case-control study conducted to date to explore the correlation between the *CLEC3A* gene polymorphisms and GC risk in the Northwestern Chinese population. We found no such risk, pointing to a need for further validation of this association in other populations. Moreover, further investigations of polymorphisms that might mediate the risk of GC would help gain a better understanding of the pathogenesis and improve prognosis in the face of the increasing incidence of gastric cancer. DECLARATIONS.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding this study.

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