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SNP at miR-483-5p-binding site in the 3'-untranslated region of the *BSG* gene is associated with susceptibility to esophageal cancer in a Chinese population

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ABSTRACT. The aim of this study was to investigate the association between a functional variant of the basigin (*BSG*) gene, caused by a polymorphism (rs11473) at the miR-483-5p binding site, and the risk of esophageal squamous cell carcinoma (ESCC) in the Chinese population. The rs11473 polymorphism was genotyped in 624 esophageal cancer patients and 636 cancer-free age- and gender-matched controls using polymerase chain reaction restriction and direct sequencing. The functional variants resulting from the *BSG* rs11473 SNP were investigated using a luciferase activity assay and validated by immunoblotting. We discovered that ESCC patients carrying the rs11473 AA genotype or A allele were at a significantly higher risk of esophageal cancer [odds ratio (OR) = 1.560, 95% confidence interval

(CI) = 1.031-2.358, P = 0.037; OR = 1.231, 95%CI = 1.038-1.459, P = 0.017, respectively] than those carrying the GG genotype and G allele. Moreover, the rs11473 polymorphism modifies the binding of miR-483-5p to basigin, as well as the basigin protein levels in esophageal cancer patients. Our data suggested that the rs11473 polymorphism at the miR-483-5p binding site in the 3'-UTR of basigin gene may play a key role in the development of esophageal cancer in a Chinese population.

Key words: Esophageal cancer; miR-483-5p; Basigin gene; Polymorphism

INTRODUCTION

Despite the considerable advances in surgery and medical technology in recent times, esophageal cancer remains a critical concern, with high morbidity and mortality. Essentially, esophageal cancer is the sixth most common cause of cancer-related death, and the eighth most common malignancy worldwide (Pennathur et al., 2013; Wen et al., 2015). More than 450,000 new cases of esophageal cancer were diagnosed worldwide in 2012 (Vaughan, 2014). Meanwhile, the 5-year survival rate of patients with esophageal cancer ranges from 15 to 25% (Enzinger and Mayer, 2003). Esophageal cancer is the fifth most common cancer and the fourth most common cause of cancer-related death in China (Chen et al., 2013; Peng et al., 2015). Excessive alcohol consumption and tobacco usage, low intake of fresh vegetables and fruits, achalasia, and low socioeconomic status have been identified as risk factors for esophageal cancer (Kamangar et al., 2009). Despite this, only a small subset of individuals exposed to the same risk factors eventually develop esophageal cancer. This indicated the possible role of genetic factors such as single nucleotide polymorphisms (SNPs) in esophageal carcinogenesis.

Cluster of differentiation 147 (CD147) or extracellular matrix metalloproteinase inducer (EMMPRIN), also known as basigin (BSG), is a highly glycosylated transmembrane protein with increased expression in many forms of malignancy (Wang et al., 2015). CD147 induces the production of matrix metalloproteinases, a group of proteins that can degrade the extracellular matrix, in adjacent interstitial normal cells (Curran and Murray, 2000; Gabison et al., 2005). Recent studies have confirmed the role of CD147 in tumor invasiveness in several human malignancies (Zou et al., 2007; Wang et al., 2010; Arendt et al., 2012; Pan et al., 2012). Moreover, inhibition of CD147 expression by RNA interference reduced the invasiveness and tumorigenicity of laryngeal carcinoma cells, while increasing its chemosensitivity to cisplatin (Zou et al., 2007). CD147 has been reported as a potential biomarker for patient prognosis (Bi et al., 2012; Zhong et al., 2013). Zheng et al. (2006) reported that an increase in CD147 expression is related to poor overall survival in gastric cancer patients. However, the correlation between CD147 and esophageal carcinogenesis remains unclear.

To our knowledge, no study has attempted to analyze the possible association between polymorphisms in the *BSG* gene and esophageal cancer. Herein, we observed increased BSG mRNA and protein levels in peripheral blood mononuclear cells (PBMCs) obtained from esophageal cancer patients. In order to understand the underlying mechanism inducing this change, we genotyped a polymorphism at the miR-483-5p binding site in the 3'-untranslated region of the *BSG* gene (rs11473). In this study, we discovered that the rs11473 polymorphism is associated with increased susceptibility to esophageal cancer in the Chinese population.

MATERIAL AND METHODS

Patients

The study protocol was approved by the Ethics Committee of the Baoji People's Hospital and the Taixing People's Hospital. A total of 624 ESCC patients from the Baoji People's Hospital and the Taixing People's Hospital and 636 gender- and age-matched control subjects were consecutively recruited to this study between January 2011 and February 2014. All participants were genetically unrelated ethnic Han Chinese from the same geographic region (Shanxi and Jiangsu Provinces, China). The diagnosis of esophageal squamous cell carcinoma (ESCC) was confirmed histologically in all patients. Patients with a primary cancer other than ESCC were excluded from this study. Furthermore, individuals with no history of transfusions 6 months prior to the study induction were excluded from the study. Individuals who smoked one cigarette per day for more than 1 year were considered as smokers, while those who consumed alcohol at least once every week were considered as drinkers. Written informed consent was obtained from all participants prior to the study. Three milliliters of peripheral blood was collected from each participant.

Genotyping

Genomic DNA was isolated from whole blood using the Blood Genomic DNA Kit (Tiangen Biotech, Beijing, China) according to the manufacturer protocols. Genotypes of SNP sites in the target genes were detected by direct sequencing of the polymerase chain reaction (PCR) product. The amplification reaction was performed in the S-1000 PCR Thermal Cycler (Bio-Rad, Hercules, CA, USA). The primer sequences used in this study are listed in Table 1. The PCR conditions were set as follows: an initial melting step at 94°C for 3 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 45 s, and a final elongation step at 72°C for 7 min. The PCR products were directly sequenced using an ABI 3500xL automated sequencer (Applied Biosystems, Foster City, CA, USA).

Table 1. Primers used in this study.

	Sequence
Forward	5'-GAGTCCACTCCCAGTGCTTG-3'
Reverse	5'-GACCCGTGGCCCTCATAAAA-3'

Detection of CD147 expression in PBMCs

CD147 expression in PBMC was determined by flow cytometry (FCM). Briefly, PBMCs were isolated and incubated with fluorescein isothiocyanate-conjugated-CD147 for 15 min. The cells were washed thrice with PBS, and subsequently analyzed using the FACSCanto II (Becton Dickinson, Franklin Lakes, NJ, USA).

Luciferase reporter assay

The BSG 3'-untranslated region (UTR)-Luc reporter assay was performed by ligating

the BSG 3'-UTR PCR product into the *Xba*I site of the pGL3 control vector (Invitrogen, Carlsbad, CA, USA). The mutant-type reporter was generated by deleting the miR-483-5p binding site. HEK293 cells were co-transfected with GG-type (pGL3-BSG-GG) or AA-type (pGL3-BSG-AA) luciferase reporters and the miR-483-5p mimic or miR-NC. After a 48-h incubation cycle, the luciferase activity was measured using the Dual Luciferase Reporter Assay System (Promega, Madison, WI, USA).

Quantitative real-time reverse transcriptase PCR (RT-PCR)

Total cellular RNA was extracted using TRIzol reagent (Invitrogen) according to the manufacturer protocols. The following primer sequences were used: CD147; forward, 5'-CCATGCTGGTCTGCAAGTCAG-3' and reverse 5'-CCGTTCATGAGGGCCTTGTC-3'; β-actin: forward 5'-CTGGAACGGTGAAGGTGACA-3' and reverse 5'-AAGGGACTTCCTG TAACAACGCA-3'. The PCR cycle conditions were set as follows: initial denaturation at 94°C for 3 min, and 40 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 45 s. The *CD147* mRNA expression was normalized to that of β-actin mRNA. The amplification was monitored on the CFX-96 real-time PCR apparatus (Bio-Rad).

Western blot analysis

The cells were harvested and lysed with ice-cold lysis buffer (Beyotime Biotechnology Inc., Haimen, China) for 30 min on ice. The lysate protein (50 μg) was separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis, and transblotted onto polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). The membrane was blocked with 5% non-fat dry milk and subsequently probed with an anti-CD147 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA) or anti-β-actin (Santa Cruz Biotechnology) antibody at 4°C overnight. The cells were then incubated with horseradish peroxidase-conjugated secondary antibodies (1:2000; Santa Cruz Biotechnology) for 1 h at room temperature. The protein bands were detected using the ECL detection system (Beyotime Biotechnology Inc.). All experiments were performed in triplicate.

Statistical analysis

All statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) software for Windows (v.12.0). Differences in the distributions of demographic characteristics, clinical variables, luciferase activity, and frequencies of rs11473 genotypes between the cases and controls were evaluated using the Student *t*-test (for continuous variables) or the χ^2 test. The controls were tested for conformance to the Hardy-Weinberg equilibrium using a goodness-of-fit χ^2 test. The association between rs11473 and ESCC risk was estimated by computing the odds ratios (ORs) and their 95% confidential intervals (CIs), using a multivariate logistic model. P values <0.05 were considered to be statistically significant.

RESULTS

Characteristics of ESCC patients and controls

The distribution of selected characteristics among ESCC patients and control subjects

is summarized in Table 2. The median age and gender distributions were not significantly different (P > 0.05), indicating adequate frequency matching. However, a greater percentage of ESCC patients smoked tobacco, consumed alcohol, and had a family history of malignancy compared to the control subjects.

Table 2. Distribution of selected characteristics among esophageal cancer patients and controls.

Variable	ESCC patients	Controls	P
	[N (%)]	[N (%)]	
	624	636	
Age (years)			0.496
≤59	268 (42.9)	286 (45.0)	
>59	356 (57.1)	350 (55.0)	
Gender			0.902
Female	186 (29.8)	192 (30.2)	
Male	438 (70.2)	444 (69.8)	
Smoking status			0.000
No	406 (65.1)	476 (74.8)	
Yes	218 (34.9)	160 (25.2)	
Drinking status			0.000
No	344 (55.1)	414 (65.1)	
Yes	280 (44.9)	222 (34.9)	
Family history of malignancy			0.000
No	530 (84.9)	588 (92.5)	
Yes	94 (15.1)	48 (7.5)	

Association between *BSG* rs11473 SNP and ESCC risk

Allele frequencies and genotype distributions of the *BSG* rs11473 SNP in ESCC patients and controls are summarized in Table 3. The observed genotype frequencies in controls and patients conform to the Hardy-Weinberg equilibrium (control subjects: $\chi^2 = 0.737$, P = 0.391; cases: $\chi^2 = 0.543$, P = 0.461). The frequencies of the GG, GA, and AA genotypes of *BSG* rs11473 were 44.9, 45.2, and 9.9% in the ESCC patients and 50.9, 41.8, and 7.2% in the control subjects, respectively. The frequency of the AA homozygote was significantly higher in ESCC patients than in the controls (9.9 *vs* 7.2%). The association between the various genotypes of the *BSG* rs11473 polymorphism and ESCC risk was determined by logistic regression analyses (Table 3). The GA genotype was not associated with ESCC risk (OR = 1.227, 95%CI = 0.973-1.546; P = 0.087) while the AA genotype was associated with increased risk of ESCC (OR = 1.560, 95%CI = 1.031-2.358, P = 0.037) in the recessive model, using the *BSG* rs11473 GG homozygote as the reference. Additionally, the rs11473 A allele carriers showed a 1.231-fold increase in ESCC risk compared to those carrying the G allele (OR = 1.231, 95%CI = 1.038-1.459; P = 0.017).

Table 3. Distribution of polymorphism rs11473 genotypes in cases and controls.

Genotypes	Cases [N (%)]	Controls [N (%)]	OR (95%CI)	P
	N = 624	N = 636		
GG	280 (44.9)	324 (50.9)		
GA	282 (45.2)	266 (41.8)	1.227 (0.973-1.546)	0.087
AA	62 (9.9)	46 (7.2)	1.560 (1.031-2.358)	0.037
G allele	842 (67.5)	914 (71.9)		
A allele	406 (32.5)	358 (28.1)	1.231 (1.038-1.459)	0.017

OR, odds ratio; CI, confidence interval.

Stratification analyses of *BSG* rs11473 SNP and risk of ESCC

We further evaluated the effect of the *BSG* rs11473 SNP on risk of ESCC, stratified by the age, gender, smoking status, drinking status, and family history of malignancy. As shown in Table 4, the association between the *BSG* rs11473 SNP and ESCC risk appeared stronger in subgroups of younger (OR = 1.498, 95%CI = 1.070-2.096; P = 0.021), male (OR = 1.405, 95%CI = 1.077-1.832; P = 0.013), non-smoking (OR = 1.407, 95%CI = 1.078-1.837; P = 0.012), non-drinking (OR = 1.430, 95%CI = 1.072-1.907; P = 0.016) patients, and those without a family history of malignancy (OR = 1.278, 95%CI = 1.010-1.617; P = 0.042).

Table 4. Stratification of the association between esophageal cancer risk and the *BSG* rs11473 SNP.

	Cases/Controls		OR (95%CI)	P
	CC	CT+TT		
Age (years)				
<59	110/146	158/140	1.498 (1.070-2.096)	0.021
≥59	170/178	186/172	1.132 (0.843-1.521)	0.452
Gender				
Males	186/226	252/218	1.405 (1.077-1.832)	0.013
Females	94/98	92/94	1.020 (0.682-1.527)	1.000
Smoking status				
No	172/242	234/234	1.407 (1.078-1.837)	0.012
Yes	108/82	110/78	1.071 (0.712-1.610)	0.756
Drinking status				
No	144/210	200/204	1.430 (1.072-1.907)	0.016
Yes	136/114	144/108	1.118 (0.786-1.590)	0.590
Family history of malignancy				
No	238/300	292/288	1.278 (1.010-1.617)	0.042
Yes	42/24	52/24	1.238 (0.617-2.485)	0.596

OR, odds ratio; CI, confidence interval.

Influence of rs11473 SNP on *BSG* expression

The rs11473 polymorphism is located at the miR-483-5p binding site in the 3'-UTR of the *BSG* gene; therefore, we attempted to identify its possible impact on the *BSG* expression in PBMCs, using real-time quantitative RT-PCR and FCM. The RT-PCR analysis showed that ESCC patients presenting the *BSG* rs11473 AA genotype expressed a higher level of *BSG* mRNA compared to patients carrying the GG genotype (P = 0.037; Figure 1A). Moreover, FCM analysis revealed that the BSG protein levels were higher in PBMCs of ESCC patients expressing the *BSG* rs11473 AA genotype than in those carrying the GG genotype (P = 0.041).

The miRNASNP 2.0 (http://www.bioguo.org/miRNASNP/) online tool was used to determine the effect of the rs11473 polymorphism on the *BSG* gene; the software indicated that this SNP destroyed an miRNA-mRNA binding site (Figure 2A). Accordingly, we cloned and transfected the luciferase reporter vector of the 3'-UTR of the *BSG* gene, expressing either the G or A allele of rs11473, into HEK293 cells. The results indicated that the activity of the reporter vector carrying the A allele was higher than that of the reporter vector carrying the G allele (P < 0.05; Figure 2B). The effect of the rs11473 SNP on BSG levels was determined by a western blot. We observed a significant increase in the BSG protein levels in AA carriers, relative to the GG carriers (P < 0.05; Figure 2C and D).

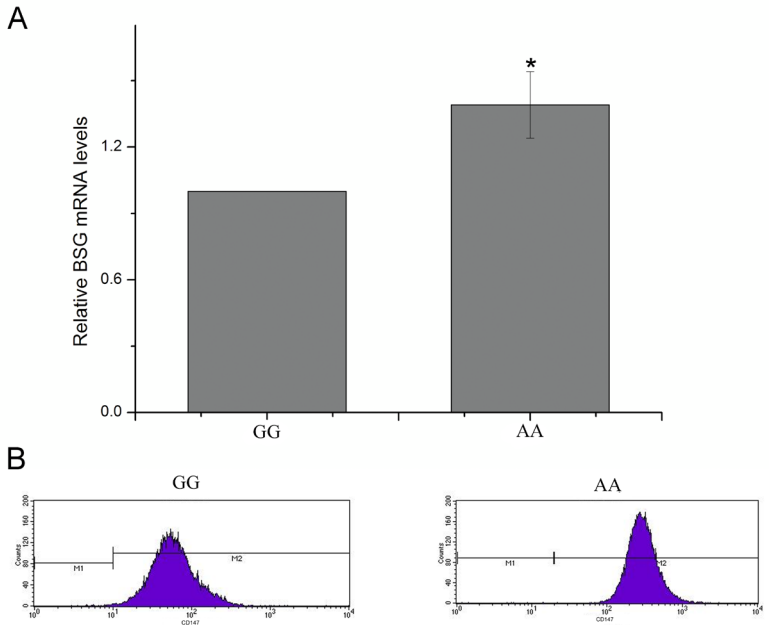

Figure 1. Effect of the rs11473 polymorphism on *BSG* expression. **A.** *BSG* mRNA levels as detected by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). **B.** BSG protein levels detected by FCM ($P < 0.05$). The polymorphism at rs11473 modified the binding of miR-483-5p to the 3'-untranslated region (UTR) of the *BSG* gene.

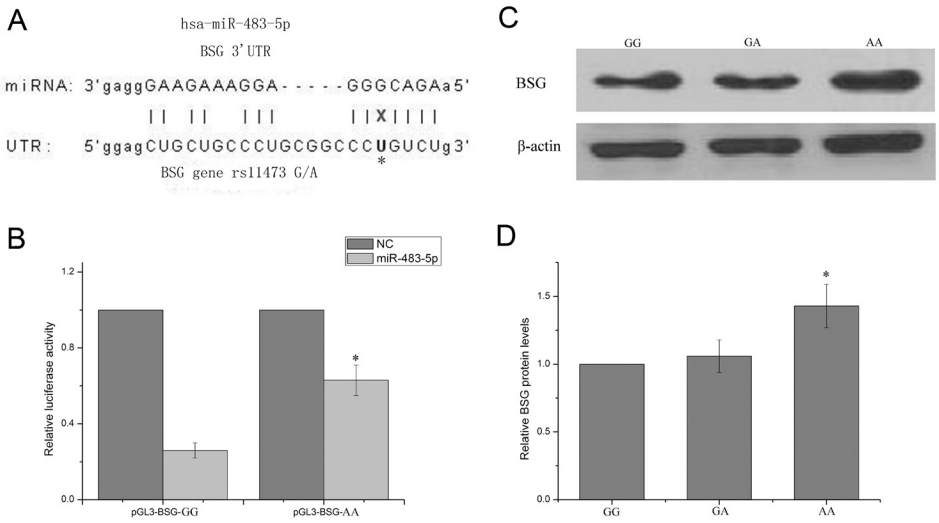

Figure 2. *BSG* rs11473 SNP modified the binding of miR-483-5p to the 3'-UTR of the *BSG* gene. **A.** miRNASNP 2.0 (http://www.bioguo.org/miRNASNP/) predicted that the rs11473 SNP created an miRNA-mRNA binding site. **B.** Luciferase activity was measured in HEK293 cells transfected with the luciferase reporter vector containing the the 3'-UTR of the *BSG* gene, presenting either the -G or -A allele of the rs11473 SNP. **C.** and **D.** BSG protein expression in PBMCs obtained from ESCC patients with different genotypes of the *BSG* rs11473 gene ($P < 0.05$).

DISCUSSION

Esophageal cancer can arise from various gene mutations related to proliferation and apoptosis. In this study, we analyzed the correlation between variants at the miR-483-5p binding site in the 3'-UTR of the *BSG* gene and the risk of ESCC. Here, we discovered that the TT genotype of rs11473 was related to a significantly increased risk of ESCC. This is the first report evaluating the relationship between SNPs in the microRNA binding site in the 3'-UTR of the *BSG* gene and susceptibility of ESCC in the Chinese population.

Many previous studies have indicated that BSG is expressed in several tissues and cells. In fact, several research groups have reported that BSG acts as a key modulator in the pathogenesis of many human diseases, including cancers, over the past 5 years. CD147 is a highly glycosylated transmembrane protein that acts as a coordinator for oncogenic cell migration and invasion via regulation of key molecular events necessary for carcinogenesis. CD147 is involved in several phases of oncogenesis, or the transformation of normal cells into tumor cells. Moreover, CD147 promotes proliferation, stimulates proteolytic enzyme expression, induces vascular endothelial growth factor expression and angiogenesis, and enables anchorage-independent growth (Bordador et al., 2000; Tang et al., 2005). For example, Wang et al. (2015) reported that CD147 plays a role in proliferation, invasion, and chemosensitivity of the human gastric cancer cell line SGC7901. Therefore, a thorough understanding the CD147 biology and proteins interacting with BSG will have a significant impact on our understanding of the development of cancer. In this study, we discovered a correlation between a polymorphism in the *BSG* gene and susceptibility of ESCC in the Chinese population. Our findings indicated that genetic factors, such as SNPs in the *BSG* gene, may play a role in esophageal carcinogenesis.

We also identified several SNPs located in the putative miRNA binding sites of cancer-related genes that significantly affect the binding capacity of putative miRNA:mRNA duplexes using bioinformatic analysis (Landi et al., 2008). Some of these SNPs have been confirmed to alter the expression of target genes by modulating the binding ability, and display a significant association with susceptibility to malignancy (Brendle et al., 2008; Naccarati et al., 2012). Ye et al. (2014) reported that SNPs in the microRNA-binding sites in the *ITGB1* and *ITGB3* 3'-UTR were associated with an increased risk of colorectal cancer. Yang et al. (2014) also reported that polymorphisms in the miR-502-binding site in the 3'-UTR of *SET8* and *TP53* may be markers indicating susceptibility to non-small cell lung cancer. Recently, Zhou et al. (2013) demonstrated that a polymorphism in an miR-191 binding site in *MDM4* is associated with increased risk of ESCC, which suggests that polymorphisms in miRNA-binding sites are hot spots that influence ESCC susceptibility. In this study, we discovered that a polymorphism at the miR-483-5p binding site in the 3'-UTR of the *BSG* gene (rs11473) modified the binding of miR-483-5p to the gene. Multivariate logistic regression analysis indicated that the rs11473 AA genotype was associated with increased risk of ESCC.

Our results demonstrated that a polymorphism at the miR-483-5p binding site in the 3'-untranslated region of the *BSG* gene is associated with increased susceptibility of esophageal cancer in a Chinese population. Additionally, these results may support the hypothesis that the miR-483-5p/*BSG* axis may play an important role in ESCC carcinogenesis. However, a major limitation of this study is the insufficient sample size.

Conflicts of interest

The authors declare no conflict of interest.

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