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ORIGINAL ARTICLE

Genetic association of promoter in GRP78 gene with nasopharyngeal carcinoma in a Chinese population

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Abstract

Background Emerging evidences were accumulated to support the view that GRP78 might be associated with multiple types of cancer. Given these, the aim of this study is to investigate the relationship between single nucleotide polymorphisms (SNPs) of *GRP78* gene promoter and nasopharyngeal carcinoma (NPC).

Methods Three SNPs (rs3216733, rs17840761 and rs17840762) in GRR78 promoter were estimated in 422 NPC patients and 452 controls. Genotyping was performed using SNaPshot SNP. Serum GRP78 level was performed by enzyme-linked immunosorbent assay (ELISA). Data were analyzed by SPSS 17.0 software.

Results Significant association between rs3216733 polymorphism and NPC was observed (Cd vs. dd: OR = 0.57, 95% CI 0.43–0.76, $P < 0.001$; CC vs. dd: OR = 0.62, 95% CI 0.39–0.98, $P = 0.043$; Cd/CC vs. dd: OR = 0.58, 95% CI 0.44–0.76, $P < 0.001$; C vs. d OR = 0.70, 95% CI 0.57–0.86, $P = 0.001$). Additionally, we further found that expression were down-regulated in serum of patients with NPC carrying rs3216733 CC genotype when compared to that of dd genotype ($P < 0.001$).

Conclusion The observations suggest that rs3216733 polymorphism in the GRP78 gene promoter may correlate with NPC susceptibility.

Keywords *GRP78*/*HSPA5* · Polymorphisms · Nasopharyngeal carcinoma · Chinese population

Introduction

Nasopharyngeal carcinoma (NPC), a complex and highly invasive malignant tumor, mainly occurs in south China, particularly in the provinces of Guangxi and Guangdong [1, 2]. NPC has a high incidence rate and difficult treatment that affects sound mind in a sound body, even the quality of daily life in patients. However, the exact cause of NPC is fully unknown, but a lot of research has identified that genetic factors and environmental triggers, such as Epstein–Barr virus (EBV) and diet, contribute to its pathogenesis [3–5]. Recent studies have revealed that genetic polymorphisms were associated with the susceptibility NPC, such as *MMP-1, APEX1, VEGF, ERCC1, HLA-A* [6–10].

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GRP78 (78-kDa glucose-regulated protein), namely *HSPA5* (heat-shock 70-kDa protein 5), is a unit of heat-shock protein 70 family and an important molecular chaperone of endoplasmic reticulum (ER) involving in the folding and assembly of proteins [11]. Previous studies have shown that reduced GRP78 increases the expression level of pro-apoptotic proteins and decreases the expression of anti-apoptotic proteins. The findings suggest that GRP78 may be a novel target spot to defeat the antagonism of radiotherapy and chemotherapy in NPC cells [12]. In addition, long noncoding RNA Hotair can promote angiogenesis by the approach of GRP78-mediated regulation of VEGFA and Ang2 expression [13]. Based upon all these points, we inferred that GRP78 might be associated with the onset of NPC.

GRP78 gene, located on chromosome 9q33-34 in humans, has a significant role in transport, folding and assembly of protein [14]. Previous work demonstrated single nucleotide polymorphisms (SNPs) in *GRP78* and the susceptibility of several cancers, including non-small cell lung cancer and hepatocellular carcinoma [15, 16]. However, as to the NPC, the genetic association has not yet

been studied until now. Therefore, this study investigated whether the promoter region of *GRP78* gene polymorphisms is correlated with NPC susceptibility in a Chinese population. Moreover, we further explore the relation of polymorphisms in serum expression.

Materials and methods

Study participants and SNP selection

The study group consisted of 422 diagnosed NPC patients who were recruited from the Affiliated Hospital of Youjiang Medical University for Nationalities (Guangxi Province, China). All NPC patients were diagnosed by histological examination. A total of 452 controls were consecutively selected from this hospital. Selection standards for control were as follows: no individual and family history of any tumors, and attending a health examination at the same period. The research was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, informed consent was obtained, and the relevant institutional review board had approved the study. The SNP selection criteria are as below: (a) minor allele frequency (MAF) > 0.05 within Han Chinese data of the HapMap database; (b) based on previous reports about the association of cancers and SNPs in *GRP78* gene promoter; (c) tagging SNPs.

Genotyping analysis

The genomic DNA was prepared from the whole peripheral blood by the standard operation of DNA isolation kit (Tianjin Inc., Beijing, China). Genotyping was carried out using SNaPshot SNP. PCR was performed under the following conditions: 95 °C for 2 min; 11cycles (94 °C for 20 min, 65 °C for 10 min, 72 °C for 1 min); 24 cycles (94 °C for 20 s, 59 °C for 30 s, 72 °C for 1 min). Then PCR products were purified by 0.5 U of shrimp alkaline phosphatase enzyme (SAP, from Promega) and 4 U of exonuclease I (EXOI, from Epicentre), incubated at 37 °C for 60 min and inactivated at 75 °C for 15 min. Then extended reaction systems (10 μL) consisted of 5 μL SNaPshot Multiplex Kit (ABI), 2 μL of the purified multiple PCR products, 1 μL of extended primer mixtures, and 2 μL ultrapure water; and 96 °C for 1 min, 28-cycle reaction (96 °C for 10 s, 55 °C for 5 s, 60 °C for 1 min); the last 4 °C in PCR instrument. This temperature is set in the PCR machine in the last step. Finally, extension products under purification with SAP were sequenced by ABI3730XL.

Table 1 Characteristics of the study population

Characteristics	NPC ($n=422$)	Controls ($n=452$)	P
Mean age (years)	46.79 ± 10.95	45.90 ± 10.72	0.234
Gender (%)			
Male	269 (63.7)	273 (60.4)	0.308
Female	153 (36.3)	179 (39.6)	
Smoking status (%)			
Yes	159 (37.7)	185 (40.9)	0.362
No	263 (62.3)	267 (59.1)	
Drinking status (%)			
Yes	152 (36.0)	175 (38.7)	0.410
No	270 (64.0)	277 (61.3)	
Tumor stage (%)			
I + II	135 (32.0)		
III + IV	287 (68.0)		
Lymph node metastasis (%)			
Yes	169 (40.0)		
No	253 (60.0)		
Distant metastasis (%)			
Yes	149 (35.3)		
No	273 (64.7)		

Serum GRP78 level assay

Serum samples were obtained from NPC patients and controls using EDTA as an anticoagulant from January 2013 to January 2016. Serum GRP78 concentration was measured by Human GRP78 ELISA kit (LifeSpan BioSciences, Inc., USA) following the instructions of the manufacturer. The optical density (OD) of the well was tested at 450-nm wavelength by an ELISA reader (RT-6000, China).

Statistical analysis

Hardy–Weinberg equilibrium (HWE) of genotype frequencies in *GRP78* was evaluated by chi-squared test. The chi-square test was utilized to assess genotype distribution and allele frequencies between cases and controls. 95% confidence interval (CI) and odds ratio (OR) were evaluated with logistic regression. Haplotype tests of three SNPs were evaluated by the SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). All calculations were used with the SPSS 17.0 software. The P value of < 0.05 was considered as statistical differences.

Results

Characteristics of the study subjects

The characteristics of the subjects in this study are presented in Table 1. The mean age of NPC patients was

46.79 years (S.D. 10.95) and 63.7% were men. The mean age in the controls was 45.90 years (S.D. 10.72) and 60.4% were men. No significant difference was observed in age, gender, smoking and drinking status between NPC patients and controls ($P > 0.05$).

Polymorphisms in GRP78 and risk of NPC

The association results of genotype and allele distributions for each SNP are shown in Tables 2 and 3. No SNPs deviated from Hardy–Weinberg equilibrium at $P > 0.05$. Distributions of genotype frequencies of rs3216733 were significantly different in the Chinese population under logistic regression (Cd vs. dd: OR = 0.57, 95% CI 0.43–0.76, $P < 0.001$; CC vs. dd: OR = 0.62, 95% CI 0.39–0.98, $P = 0.043$; Cd/CC vs. dd: OR = 0.58, 95% CI 0.44–0.76, $P < 0.001$). Moreover, allele frequencies were significantly different between NPC patients and controls (C vs. d adjusted OR = 0.70, 95% CI 0.57–0.86, $P = 0.001$). Insignificant differences in polymorphisms existed between NPC patients and controls for other SNPs (all $P > 0.05$).

Serum GRP78 level and rs3216733 polymorphisms

As shown in Fig. 1a, serum level analyses of GRP78 were examined in NPC patients and controls. The analysis showed that the levels of GRP78 were higher in NPC patients compared with controls ($P < 0.001$). In addition, we further

Table 2 Genotype distributions of three SNPs in *GRP78* between NPC patients and controls

Genotype	NPC ($n = 422$)	Controls ($n = 452$)	[a]OR (95% CI)	[a]*P*	OR (95% CI)	*P*
rs3216733						
dd	219 (51.9)	176 (38.9)	1 (Ref)		1 (Ref)	
Cd	162 (38.4)	224 (49.6)	0.57 (0.43–0.76)	< 0.001	0.58 (0.43–0.77)	< 0.001
CC	41 (9.7)	52 (11.5)	0.62 (0.39–0.98)	0.043	0.63 (0.40–0.99)	0.048
Cd/CC	203 (48.1)	276 (61.1)	0.58 (0.44–0.76)	< 0.001	0.59 (0.45–0.77)	< 0.001
Cd/dd	381 (90.3)	400 (88.5)	1.22 (0.79–1.89)	0.367	1.21 (0.78–1.86)	0.391
rs17840761						
GG	120 (28.4)	127 (28.1)	1 (Ref)		1 (Ref)	
GA	200 (47.4)	228 (50.4)	0.93 (0.68–1.28)	0.691	0.92 (0.67–1.27)	0.642
AA	102 (24.2)	97 (21.5)	1.11 (0.76–1.62)	0.557	1.11 (0.76–1.61)	0.575
GA/AA	302 (71.6)	325 (71.9)	0.99 (0.73–1.33)	0.960	0.98 (0.73–1.32)	0.912
GA/GG	320 (75.8)	355 (78.5)	0.86 (0.63–1.18)	0.347	0.86 (0.62–1.17)	0.340
rs17840762						
G/G	285 (67.5)	331 (73.2)	1 (Ref)		1 (Ref)	
G/A	127 (30.1)	112 (24.8)	1.32 (0.98–1.79)	0.065	1.31 (0.97–1.77)	0.071
A/A	10 (2.4)	9 (2.0)	1.29 (0.51–3.23)	0.584	1.29 (0.51–3.22)	0.584
GA/AA	137 (32.5)	121 (26.8)	1.32 (0.98–1.77)	0.059	1.31 (0.98–1.76)	0.065
GA/GG	412 (97.6)	443 (98.0)	0.84 (0.34–2.09)	0.704	0.84 (0.34–2.08)	0.701

OR odds ratio, *95% CI* 95% confidence interval, *Ref* reference

[a]Adjusted by age, gender smoking and drinking

Table 3 Allele distributions of three SNPs in *GRP78* between NPC patients and controls

Allele	NPC $n = 422$ (%)	Controls $n = 452$ (%)	[a]OR (95% CI)	[a]*P*	OR (95% CI)	*P*
rs3216733						
d	600 (71.1)	576 (63.7)	1 (Ref)		1 (Ref)	
C	244 (28.9)	328 (36.3)	0.70 (0.57–0.86)	0.001	0.71 (0.58–0.87)	0.001
rs17840761						
G	440 (52.1)	482 (53.3)	1 (Ref)		1 (Ref)	
A	404 (47.9)	422 (46.7)	1.05 (0.87–1.27)	0.599	1.05 (0.87–1.27)	0.620
rs17840762						
G	679 (82.6)	774 (85.6)	1 (Ref)		1 (Ref)	
A	147 (17.4)	130 (14.4)	1.26 (0.97–1.63)	0.076	1.28 (0.99–1.67)	0.053

OR odds ratio, *95% CI* 95% confidence interval, *Ref* reference

[a]Adjusted by age, gender smoking and drinking

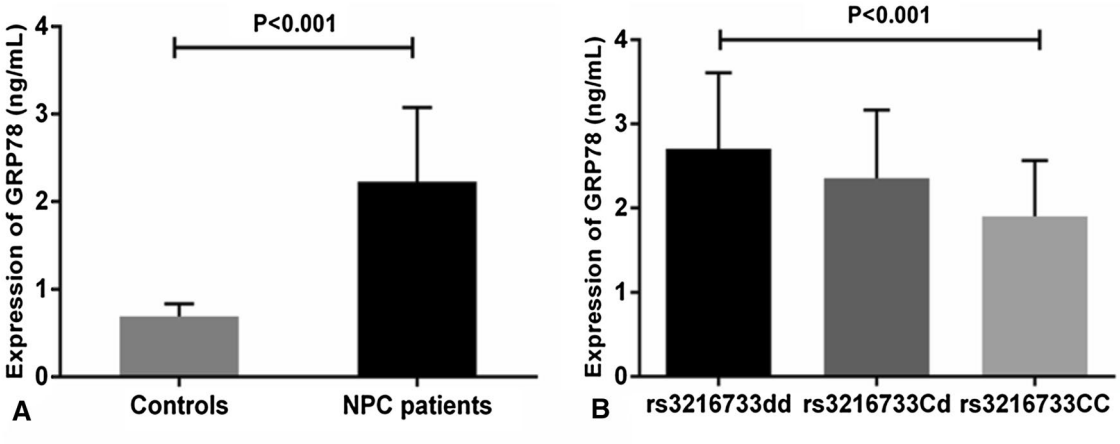

Fig. 1 **a** Serum level of GRP78 in NPC patients and controls. **b** Serum level of GRP78 in patients carrying rs3216733 CC genotypes and patients carrying dd genotype

detected that NPC patients carrying rs3216733 CC genotypes presented lower levels of GRP78 than those of dd genotype ($P < 0.001$, Fig. 1b).

Haplotype analysis of the GRP78 gene

Four main haplotypes for *GRP78* gene were identified by online SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). The largest proportion haplotype (d-A-G) accounted for 46.8% and 44.6% in NPC and controls, respectively (Table 4). The results revealed that the haplotypes C–G–G and d–G–A were significantly related to NPC (OR = 0.74, 95% CI 0.59–0.92, $P = 0.006$; OR = 1.35, 95% CI 1.02–1.79, $P = 0.037$, respectively).

rs3216733 polymorphism and clinical features

To examine the potential relationship of polymorphisms and the clinical features of NPC, we conducted the ELISA analysis and summarized the results in Table 5. No significant association between rs3216733 polymorphism in *GRP78* and clinical features of the NPC was observed ($P > 0.05$).

Discussion

Cancer cells are characterized by change of glucose metabolism, and impaired blood flow and hypoxia in the tumor microenvironment, all of which can result in ER stress [17, 18]. GRP78 has special functions in the ER where it can promote the folding, maturation and assembling of newly formed proteins and also coordinate the unfolded protein response (UPR) [19, 20]. Some studies reported that GRP78 plays an important mediator in cancer mechanism, such as tumor survival and proliferation, angiogenesis, and metastasis [21]. GRP78 was the hallmark of ER stress. Liu et al. found that Tetrandrine induces the death of apoptotic cell through ER stress in NPC-TW 039 cells, and the protein expression of GRP78 increased [22]. In addition, Lin et al. indicated the results that Tetrandrine enhanced ER stress-interrelated protein expression such as GADD153, GRP78, ATF-6 α and ATF-6 β, and pointed out ER stress may be a potential role in the treatment of cancers [23]. Li et al. indicated that the expression of GRP78 protein was inhibited by triptolide treatment [24]. Radiotherapy and chemotherapy are the major treatment approaches to kill cancer cells for NPC patients. Recently, Huang et al. revealed that the resistance of IR and DDP in the NPC cells was reversed by

Table 4 Haplotype analysis of the *GPR78* polymorphisms with risk of NPC

Haplotype	NPC $2n = 844$ (%)	Controls $2n = 904$ (%)	OR (95% CI)	*P*
d–A–G	395 (46.8)	403 (44.6)	1 (Ref)	
C–G–G	236 (28.0)	327 (36.2)	0.74 (0.59–0.92)	0.006
d–G–A	147 (17.4)	111 (12.3)	1.35 (1.02–1.79)	0.037
d–G–G	58 (6.9)	44 (4.9)	1.34 (0.89–2.04)	0.161

Haplotype with frequency less than 3% will not be considered in the statistical analysis

OR odds ratio, *95% CI* 95% confidence interval, *Ref* reference

Table 5 Genotype frequencies of rs3216733 in relation to clinical parameters of NPC patients

Items	NPC $n=422$ (%)		[a]OR (95% CI)	[a]*P*	OR (95% CI)	*P*
Tumor stage	I + II	III + IV				
dd	77 (57.0)	142 (49.5)	1 (Ref)		1 (Ref)	
Cd	49 (36.3)	113 (39.4)	0.51 (0.23–1.13)	0.095	0.80 (0.52–1.25)	0.314
CC	9 (6.7)	32 (11.1)	0.62 (0.27–1.40)	0.751	0.52 (0.24–1.14)	0.099
Cd/CC	58 (43.0)	145 (50.5)	1.33 (0.88–2.02)	0.174	1.36 (0.90–2.05)	0.147
Cd/dd	126 (93.3)	255 (88.9)	0.55 (0.254–1.20)	0.132	0.57 (0.26–1.23)	0.147
Lymph node metastasis	Yes	No				
dd	85 (50.3)	134 (52.9)	1 (Ref)		1 (Ref)	
Cd	68 (40.2)	94 (37.2)	1.13 (0.75–1.72)	0.560	1.14 (0.75–1.73)	0.534
CC	16 (9.5)	25 (9.9)	1.01 (0.51–2.01)	0.978	1.01 (0.51–2.00)	0.980
Cd/CC	84 (49.7)	119 (47.1)	1.11 (0.75–1.64)	0.614	1.12 (0.76–1.65)	0.591
Cd/dd	153 (90.5)	164 (90.1)	1.04 (0.54–2.03)	0.899	1.46 (0.75–2.84)	0.265
Distant metastasis	Yes	No				
dd	71 (47.7)	148 (54.2)	1 (Ref)		1 (Ref)	
Cd	61 (40.9)	101 (37.0)	1.26 (0.82–1.94)	0.287	1.26 (0.82–1.93)	0.288
CC	17 (11.4)	24 (8.8)	1.51 (0.76–3.00)	0.241	1.48 (0.75–2.92)	0.261
Cd/CC	78 (52.3)	125 (45.8)	1.31 (0.88–1.96)	0.190	1.30 (0.87–1.94)	0.197
Cd/dd	132 (88.6)	249 (91.2)	0.73 (0.38–1.42)	0.357	0.75 (0.39–1.44)	0.385

OR odds ratio, *95% CI* 95% confidence interval, *Ref* reference

[a]Adjusted by age, gender smoking and drinking

the inhibition of GRP78 protein by PI/Annexin V staining. Moreover, knockdown of GRP78 can regulate the expression of pro-apoptotic proteins and anti-apoptotic proteins [12]. Thus, these evidences revealed that GRP78 involved the pathologic process in NPC.

In the current study, this is the first report to explore potential susceptible of SNPs (rs3216733, rs17840761 and rs17840762) of the promoter in *GRP78* in risk of NPC. Interestingly, we found significant associations between rs3216733 polymorphisms in *GRP78* gene and NPC. The results indicated that the rs3216733 polymorphism was related to a decreased NPC risk in Cd genotype, CC genotype, Cd/CC genotype and C allele (Cd vs. dd: OR = 0.57, 95% CI 0.43–0.76, $P < 0.001$; CC vs. dd: OR = 0.62, 95% CI 0.39–0.98, $P = 0.043$; Cd/CC vs. dd: OR = 0.58, 95% CI 0.44–0.76, $P < 0.001$; C vs. d OR = 0.70, 95% CI 0.57–0.86, $P = 0.001$). Furthermore, we found that the serum level of GRP78 was up-regulated in NPC patients and rs3216733 genotypes related to the expression of GRP78. These findings provide new insights that rs3216733 probably may be a regulatory factor in the expression of serum GRP78. These preliminary findings demonstrated that rs3216733 may contribute to NPC susceptibility, probably by affecting the expression of GRP78.

A previous study has identified that polymorphisms in *GRP78* promoter were found to influence the activity of *GRP78* promoter [25]. The promoter of *GRP78* possesses three ER stress response elements (ERSEs) which have a special tripartite structure CCAATN 9 CCACG, with N being 9-bp GC-rich region [26]. Furthermore, transcription factors (CBF/NF-Y, YY1 and TFII-I) can activate the ERSE by binding to the CCAAT, CCACG and GC-rich N9 region [27]. Hsu et al. [28] investigated the association of the *GRP78* promoter polymorphisms and Alzheimer's disease (AD) risk. The *GRP78* transcriptional activity of the C allele in rs3216733 was obviously lower than that of del allele. Finally, their results revealed that C allele has a protective role in Taiwanese AD susceptibility. Similar to the association, we found that allele and genotype of rs3216733 decreased risk of NPC. Zhu et al. [29] compared *GRP78* polymorphisms in chronic HBV carriers and healthy subjects. However, lack of significant associations was detected in polymorphism analysis of rs17840761 and rs17840762. Subsequently, Liu et al. [30] have reported that rs17840761 and rs17840762 polymorphisms in *GRP78* gene do not relate to type 2 diabetes (T2D). Consistent with these results, our result showed that the two SNP polymorphisms are not associated with the NPC risk.

To the best of our knowledge, our observations first provide novel viewpoints in *GRP78* to NPC risk and create an evidence to understand the strategies of diagnosis and treatment. But several possible limitations of the current study should be discussed. First of all, we only explored three polymorphisms (rs3216733, rs17840761 and rs17840762) in *GRP78* gene. Thus, it is far away to prove the whole gene with NPC risk and more studies are essential. Second, NPC is affected by complex some environmental factors, viruses, some foods, nicotine, etc. In the current study, the

relationship of their interaction cannot be estimated. To provide more powerful evidences for *GRP78* in the etiology of NPC in the future studies, further interaction of gene and environment should be performed.

In conclusion, our results suggested that rs3216733 in *GRP78* promoter may decrease NPC susceptibility. Functional analysis of rs3216733 is needed to elucidate the molecular mechanism in NPC. It is prospective that more studies will be used to explore the role of this SNP in cell and animal experiments. In addition, newly developed direction is its effect on the severity and survival status of NPC, which will help us to prove it as a marker of NPC.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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