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Original Article

No association of *VAMP8* gene polymorphisms with glioma in a Chinese Han population

Ping Zhou[1], Shuo Zhang[2], Hongyan Chen[2], Yuanyuan Chen[2], Xiaodong Liu[1], Bing Sun[1]

[1]*Department of Neurosurgery, Shanghai Neurosurgical Center, Huashan Hospital, Fudan University, Shanghai, China;* [2]*State Key Laboratory of Genetic Engineering and MOE Key Laboratory of Contemporary Anthropology, School of Life Sciences and Institutes for Biomedical Sciences, Fudan University, Shanghai, PR China*

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Abstract: Vesicle-associated membrane protein 8 (*VAMP8*) gene plays an important role in biological functions like endosomal fusion, sequential granule-to-granule fusion and autophagy. The current research identified *VAMP8* acted as a novel oncogene by promoting cell proliferation and therapeutic resistance in glioma. Nevertheless, the association between *VAMP8* genes polymorphism and glioma patients has not been well studied. In our study, to explore the association between single nucleotide polymorphisms (SNPs) of *VAMP8* gene with glioma risk in the Chinese Han population, we performed a hospital based case-control study (992 cases and 1008 controls). Eight common tagging SNPs of *VAMP8* gene were genotyped, while no significant difference in allele or genotype frequency was found between glioma patients and healthy controls. No positive linkage disequilibrium (LD) was detected either. No haplotype distribution was positive. Accordingly, our study suggested that *VAMP8* gene variants might not contribute to glioma susceptibility and associated with glioma in the Chinese Han population.

Keywords: *VAMP8* gene, polymorphisms, genetic susceptibility, molecular biology, glioma

Introduction

Glioma, arising from glial or precursor cells, is one of the most common brain tumors with the incidence rate of 6.02 per 100,000 [1]. The broad category glioma accounted for nearly 28% of all brain tumors and 80% for malignant brain tumors [1]. Malignant gliomas, the most frequent and deadly malignant brain tumors, are second only to stroke as the leading cause of death from neurological diseases. Despite the development of aggressive surgery, radiation and chemotherapy, and the improvement of diagnosis and detection ability in recent years, the prognosis of glioma still remains dismal and the survival from malignant gliomas remains poor with a median survival time on average 14 months for patients with glioblastoma following diagnosis [2]. Previous studies of gliomas, as well as of other types of cancer, suggested that gliomas might arise from a combination of inherited genetic variation and differential environmental exposures. Previous candidate-gene association studies have revealed several loci that are associated with glioma risk. These include the DNA repair genes PRKDC (also known as XRCC7) [3], XRCC1 [4], PARP1 [5], MGMT [6], ERCC1 and ERCC2 [7]; the cell cycle gene EGFt61 [8]; and the inflammation gene IL13 [9]. However, as the complexity nature of glioma, it still needs the discoveries of more susceptible regions within human genome to provide references for clinical prediction, diagnose and treatment of glioma.

Soluble NSF (nethylmaleimide-sensitive factor) receptor (SNARE) is a superfamily of small proteins with different sizes and primary structures [10]. As an essential mechanism for cellular activities, it's observed SNARE involved in the progression of various tumors, such as non-small cell lung cancer [11, 12]. Vesicle-associated membrane protein 8 (*VAMP8*) was first identified as an endosomal SNARE and has been revealed to participate in biological functions like endosomal fusion [13], the exocytosis of GLUT4 and insulin [14, 15], sequential granule-to-granule fusion [16] and autophagy [17]. More important, Chen et al recently identified *VAMP8* acted as a novel oncogene in glioma by

Table 1. Distribution of demographic variables in glioma cases and controls

	No. of Cases	%	No. of Controls	%	*P*[a]
Demographics					
Total	992		1008		
Sex					0.99
Male	593	59.8	603	60.9	
Female	394	39.7	401	38.7	
Missing	5	0.5	4	0.4	
Age					0.64[b]
Mean ± SD	44.25±15.73		45.18±18.62		
Smoke status					0.99
Never	586	59.1	593	58.8	
Ever	209	20.7	213	21.1	
Current	188	19.0	192	19.1	
Missing	9	1.0	10	1.0	
Family History of Cancer					0.003
No	723	72.9	781	77.5	
Yes	163	16.4	120	11.9	
Missing	106	10.7	107	10.6	
Histological types					
Glioblastoma	326	32.9			
Other gliomas[c]	666	67.1			

The significant differences are indicated in bold. [a]Two-sided χ^2 test. [b]Independent-samples T-test. [c]Other gliomas including oligodendrogliomas, ependymomas or mixed glioma.

promoting cell proliferation and therapeutic resistance [18]. While, the association between *VAMP8* gene polymorphisms and glioma has not been well studied.

To date, fewer studies have examined the susceptibility of *VAMP8* gene with diseases, and no association studies have been done between *VAMP8* polymorphisms and glioma. Therefore, to identify the association between genetic polymorphism of *VAMP8* and glioma risk, the authors performed a hospital-based case-control study in a Chinese Han population.

Methods and materials

Patients selection

992 patients histopathologically diagnosed with glioma were from the Department of Neurosurgery at Huashan Hospital (Shanghai, China) between October 2007 and July 2013. And, pathological diagnoses and demographic data of all eligible cases were validated by trained abstractors. All control subjects were randomly selected from trauma outpatients and annual check-up visitors at the same hospital during the similar time period and frequency matched to cases by sex, age (±5 years) and residence (urban or rural areas). The controls with a self-reported history of cancer or central nervous system-related diseases or previously receiving radiotherapy\chemotherapy for certain diseases were excluded. All cases and controls in this study were genetically from Shanghai and its surrounding regions (Jiangsu, Anhui and Zhejiang provinces) in eastern China with a Han Chinese ethnic background.

At recruitment, written informed consent was obtained from each subject and the detailed demographic information, including demographic factors, smoking status, family history of cancer and other lifestyle factors, were collected by trained nurses. For childhood glioma patients under the age of 18 years, baseline data were collected from their parents or other relatives. After interview, ~3-5 ml peripheral venous blood sample were collected from each subject for DNA extraction and genotyping. Our research protocol was approved by the Ethics Committee for Human Subject research of Fudan University.

Selection of tagging SNPs and genotyping assays

We based the r^2 statistic to find tagging SNPs according to the HapMap database (http://www. hapmap.org/, phase III Aug10, on NCBI B36 assembly, dbSNP b132; population: Han Chinese in Beijing, China) on the basis of pairwise linkage disequilibrium (LD) r^2 threshold of 0.8. A total of eight tagging SNPs in this region were selected for this study.

We used the white blood cell fractions of the whole blood samples for extraction of genomic DNA using the Qiagen Blood Kit (Qiagen,

Table 2. Information of 8 genotyped SNPs of gene *VAMP8*

SNP ID	Chromosome	Chromosome position	SNP location[a]	Base change	Minor allele frequency			Genotyping rate (%)	*P*-value for HWE[c]	*P*-value for χ^2	OR (95% CI)[d]
					Database[b]	Control	Case				
rs3770098	2	85658878	intron	G/A	0.325	0.305	0.315	97.6%	0.31	0.536	0.95 (0.81-1.11)
rs7579147	2	85659165	intron	A/G	0.292	0.262	0.268	100%	0.88	0.711	0.97 (0.83-1.34)
rs3731828	2	85659777	synonymous	A/G	0.244	0.262	0.268	99.9%	0.92	0.711	0.97 (0.83-1.34)
rs1348818	2	85660593	intron	A/G	0.307	0.305	0.315	100%	0.16	0.536	0.95 (0.82-1.11)
rs13421434	2	85661121	intron	A/G	0.033	0.043	0.047	99.9%	0.44	0.555	0.90 (0.64-1.27)
rs1009	2	85662248	synonymous	A/G	0.305	0.305	0.316	100%	0.15	0.536	0.95 (0.82-1.11)
rs1058588	2	85662382	3' UTR	A/G	0.305	0.305	0.316	100%	0.15	0.536	0.95 (0.82-1.11)
rs1010	2	85662493	3' UTR	A/G	0.304	0.305	0.315	99.9%	0.17	0.562	0.96 (0.82-1.13)

Abbreviations: *VAMP8*, vesicle-associated membrane protein 8: SNP, single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium. The significant differences are indicated in bold. [a]SNP location in National Center for Biotechnology Information Genome build 37.3 (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?). [b]Minor allele frequency from dbSNP databases. [c]HWE *P*-value in control group. [d]Adjusted for gender, age, smoke and family history of cancer.

Chatsworth, CA), according to the manufacturer's instructions. Fragments containing polymorphisms were amplified by the PCR and genotyped with Sequenom MassARRAY iPLEX platform using allele-specific matrix-assisted laser desorption ionization-time-of-flight mass spectrometry assay [19]. We examined genotyping quality by means of a detailed quality control procedure that ensured over 95% successful call rate with duplicate calling of genotypes, internal positive control samples.

Statistical analysis

SPSS software (SPSS, Chicago, IL) was used for statistical analyses. The χ^2 test was used to compare the differences in demographic characteristics including sex, smoking statues, family history of cancers, and also frequency distributions of genotypes and alleles between cases and controls. Unconditional logistic regression analysis was performed to calculate ORs and 95% CIs as estimates of the relative risk for each SNP, with adjustment for family history of cancers. All SNPs were required genotyping rate ≥0.95. All *P*-values presented were two-sided test, and the level of $P \leq 0.05$ was considered significant. Haploview software V4.2 was used to assess *P*-value of HWE and genotyping rate, HWE was performed only among controls, genotyping rate was performed both cases and controls.

The pairwise linkage disequilibrium (LD) among the SNPs was examined using Lewontin's standardized coefficient D' and LD coefficient r2 [20], and Haplotype blocks were assessed by the Haploview software given by Gabriel et al [21]. To account for haplotype ambiguity, the statistical significance of the performed global and haplotype-specific tests (haplo.score) was expressed as a permutation *P* value (minimal simulation: 10,000 with a significance level <0.05) [22].

Results

The distribution of demographic characteristics of the 992 cases and 1008 controls were presented in **Table 1**. The mean ± SD of age was 44.25±15.73 for cases and 45.18±18.62 for controls. Approximately 60% of both cases and controls were male, corresponding to the previous study [23]. Cases were more likely to report a family history of cancer (among first-degree relatives) than controls (*P*=0.003), and the smoke status between cases and controls were no significant difference. The histological subtypes were also presented.

Our statistics analysis found the allele and genotype distributions show no any significant difference in all the eight SNPs between control and patients. The difference was also not observed in the dominant model with multivariate logistic regression analysis, which is shown in **Tables 2** and **3**. All SNPs were in Hardy-Weinberg equilibrium in control subjects, the *P* value were more than 0.05.

The LD plot was shown in **Figure 1**. One block was defined, the logistic regression analysis revealed the haplotype was not significant associated with glioma risk either, even after 10000 time permutation test. The results were shown in **Table 4**. All these results suggested that the *VAMP8* polymorphisms were not associated with the glioma risk.

Table 3. Genotype frequencies of SNPs between cases and controls and their associations with glioma risk

SNP ID	Genotype	No. of cases	%	No. of controls	%	*P*-value for χ^2 test[a]	Logistic regression[a]	
							OR (95% CI)	*P*-value[a]
rs3770098	CC	358	36.1	370	36.71	0.98	1.00 (reference)	
	AC	472	47.6	475	47.12		1.03 (0.85-1.25)	0.79
	AA	135	13.6	143	14.19		0.98 (0.74-1.29)	0.86
Dominant	CC/AC+AA	607	61.2	618	61.31	0.87	1.02 (0.85-1.22)	0.87
rs7579147	GG	429	43.2	434	43.06	0.97	1.00 (reference)	
	AG	441	44.46	457	45.34		0.98 (0.81-1.18)	0.80
	AA	121	12.20	117	11.61		1.05 (0.79-1.39)	0.76
Dominant	GG/GA+AG	562	56.65	574	56.94	0.92	0.99 (0.83-1.18)	0.92
rs3731828	CC	429	43.25	433	42.96	0.98	1.00 (reference)	
	TC	441	44.46	457	45.34		0.97 (0.81-1.17)	0.78
	TT	120	12.10	117	11.61		1.04 (0.78-1.38)	0.81
Dominant	CC/TC+TT	561	56.55	574	56.94	0.88	0.99 (0.83-1.19)	0.88
rs1348818	TT	361	36.39	370	36.71	0.99	1.00 (reference)	
	AT	490	49.40	492	48.81		1.02 (0.84-1.24)	0.83
	AA	141	14.21	146	14.48		0.99 (0.75-1.30)	0.94
Dominant	TT/AT+AA	631	63.61	638	63.29	0.88	1.01 (0.85-1.22)	0.88
rs13421434	CC	903	91.03	916	90.87	0.97	1.00 (reference)	
	AC	85	8.57	91	9.03		0.95 (0.70-1.29)	0.73
	AA	1	0.10	1	0.10		1.01 (0.06-16.2)	0.99
Dominant	CC/AC+AA	86	8.67	92	9.13	0.74	0.95 (0.70-1.29)	0.74
rs1009	AA	361	36.39	369	36.61	0.99	1.00 (reference)	
	GA	490	49.40	492	48.81		1.02 (0.84-1.23)	0.86
	GG	141	14.21	146	14.48		0.99 (0.75-1.30)	0.93
Dominant	AA/GA+GG	631	63.61	638	63.29	0.91	1.01 (0.84-1.21)	0.91
rs1058588	CC	361	36.39	369	36.61	0.99	1.00 (reference)	
	TC	490	49.40	492	48.81		1.02 (0.84-1.23)	0.86
	TT	141	14.21	146	14.48		0.99 (0.75-1.30)	0.93
Dominant	CC/TC+TT	631	63.61	638	63.29	0.91	1.01 (0.85-1.21)	0.91
rs1010	TT	361	36.39	369	36.61	0.99	1.00 (reference)	
	CT	490	49.40	490	48.61		1.02 (0.84-1.24)	0.82
	CC	141	14.21	146	14.48		0.99 (0.75-1.30)	0.93
Dominant	TT/CT+CC	631	63.61	636	63.10	0.88	1.01 (0.85-1.22)	0.88

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. The significant differences are indicated in bold. [a]Adjusted for gender, age, smoke and family history of cancer.

Discussion

In this case-control study, we examined eight SNPs (rs3770098, rs7579147, rs3731828, rs1348818, rs13421434, rs1009, rs1058588 and rs1010) from 992 glioma patients and 1,008 controls in Chinese population. According to the observed results, there was no positive association between *VAMP8* gene and glioma.

VAMP8 is a member of SNARE family, which is a superfamily of small proteins with different sizes and primary structures. *VAMP8* has been reported to play multiple roles of in diverse cellular activities like endocytosis [Endobrevin, a novel synaptobrevin/VAMP-like protein preferentially associated with the early endosome], exocytosis [Dual role of *VAMP8* in regulating insulin exocytosis and islet beta cell growth], granule fusion [*VAMP8* is a SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) selectively required for sequential granule-to-granule fusion] and

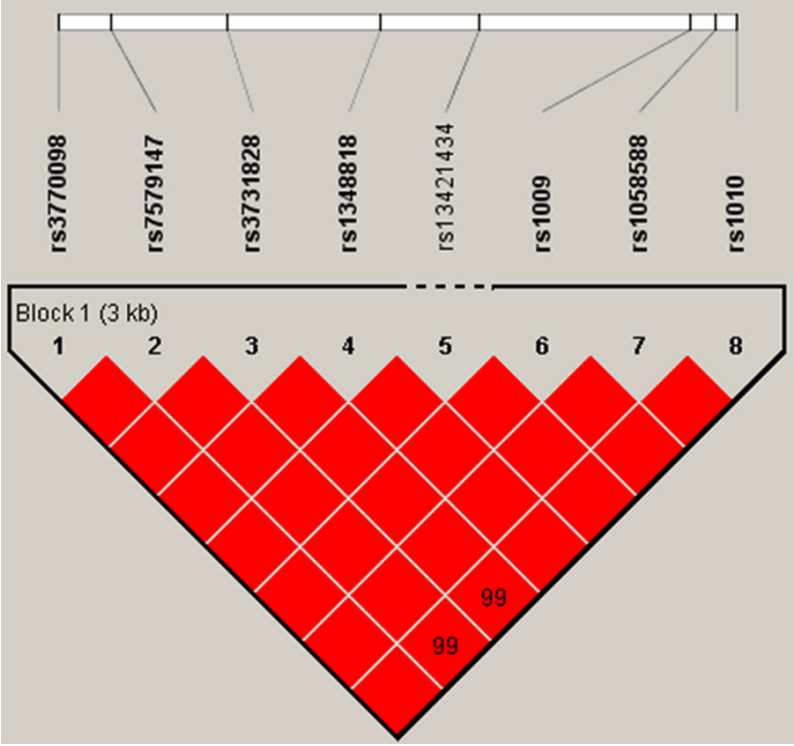

Figure 1. A schematic view of associations between SNPs and glioma risk.

autophagy [The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes]. Loss of *VAMP8* could suppress the normal physiological activities of cells. More importantly, the recent study demonstrated its roles in the prediction of the prognosis and chemotherapy treatment efficacy for glioma patients as well as its regulatory functions in the progression and temozolomide sensitivity of glioma cells. Therefore, we tried to find whether there were any SNPs within the gene region of *VAMP8* that were responsible for glioma risk.

In our study, all of these SNPs were in Hardy-Weinberg equilibrium in our samples, but we failed to observe any statistical significance neither in allele and genotypes frequencies of the SNPs nor in the frequency distributions of haplotypes between cases and controls in *VAMP8* gene and glioma risk. Among the genotyped SNPs, the current knowledge about the first seven is rather limited since there are no reports indicating their possible roles in any biological activities and diseases. Nevertheless, as to rs1010, the eighth one we detected in our study, there are pieces of evidences showing that it is significantly associated with the risk of non-cardioembolic stroke [24], coronary heart disease [24, 25], preeclampsia [26] and platelet reactivity [27]. However, there are also controversies arguing against its roles in platelet functions [28] and association with heart disease risk in the elderly [29], which render its precise functions in the aforementioned disorders elusive.

Probably, the following limitations and reasons might be responsible for the results in this study: First, the sample size in this study is not big enough. Despite the number of samples is 2,000, larger number of samples should be incorporated into the study to reach more statistical power. Moreover, samples from different races and meta-analyses are also needed to further test the association; second, the SNP coverage in the present study is also limited. Genetic analyses with more functional SNPs and saturated SNP coverage of the gene region of *VAMP8* are necessary to fully reflect the contributions of *VAMP8* to glioma risk; third, these results might imply that *VAMP8* does not participate in the initiation process of glioma. Despite previous reported functions of *VAMP8* in glioma development and temozolomide sensitivity regulation, it does not demonstrate its role in the initiation of glioma. It is possible that *VAMP8* itself does not involve in the onset but in the maintenance and progression of glioma, which makes it less likely to exhibit any significant association in glioma risk between the case and control samples. In addition, although our result does not support the association of *VAMP8* with glioma, it does not exclude the possibility that this gene confers genetic susceptibility to glioma in other population.

In conclusion, our study found no significant association between the SNPs in *VAMP8* gene region and glioma risk, indicating that these

Table 4. Frequency distributions of haplotypes in each block in *VAMP8*, and association with glioma risk

Haplotype[a]	Overall					
	Case (%)	Control (%)	*P*-value for χ^2 test[b]	Logistic regression		Global score test[c]
				OR (95% CI)[b]	*P*-value[b]	
Block			0.99			χ^2 = 0.1120, df = 2,
CGCTACT	606 (0.611)	616 (0.611)		1.00 (reference)		*p*-value = 0.912,
AATAGTC	341 (0.344)	346 (0.343)		1.00 (0.83-1.21)	0.99	sim[b] = 0.940
AGCAGTC	45 (0.045)	46 (0.046)		0.99 (0.65-1.52)	0.97	

Abbreviations: OR, odds ratio; CI, confidence interval. [a]Polymorphic bases were in 5'-3' order listed in **Table 1**. [b]Adjusted for gender, age, smoke and family history of cancer. [c]Generated by permutation test with 10000 times simulation.

variants might not contribute to glioma susceptibility in the Chinese Han population. Although the negative results, the studies based on more SNPs of *VAMP8* or other important members of SNARE in glioma as well as other diseases would be worthwhile. And our data may provide a reference for further studies on the role of the gene in other populations.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bing Sun, Department of Neurosurgery, Shanghai Neurosurgical Center, Huashan Hospital, Fudan University, Shanghai, China. Tel: +86 21 52887223; E-mail: msunbing@yahoo.com

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