Research Square

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Role of PVT1 Polymorphisms in the Glioma Susceptibility and Prognosis

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Abstract

Background: Genetic factors play a crucial role in the glioma risk and prognosis of glioma patients. To explore the role of PVT1 polymorphism in the susceptibility and survival of glioma in the Chinese Han population, we conducted a case-control study.

Methods: The three single-nucleotide polymorphisms (SNPs) in PVT1 were genotyped using Agena MassARRAY from 575 patients with glioma and 500 healthy controls. We used the χ 2 test to analyze the differences in distribution of allele and genotype between the cases and controls. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated by logistic regression analysis to evaluate the association SNPs with glioma risk. The effects of polymorphisms and clinical features on survival of glioma patients were evaluated using the log-rank test, Kaplan-Meier and Cox regression analysis.

Results: We found that rs13255292 was associated with a decreased risk of glioma in the recessive model in overall or male; and rs4410871 was significantly associated with an increased the risk of glioma in age≤40 years old or female. Moreover, the extent of resection and chemotherapy were found to be key prognostic factors in survival of glioma patients. However, the gender, age, tumor grade, radiotherapy and PVT1 polymorphisms have no effect on prognosis of glioma patients.

Conclusions: Our results indicated that PVT1 polymorphisms (rs13255292 and rs4410871) were associated with glioma susceptibility, but have no effect on prognosis of glioma patients. Further studies with large samples are required to confirm the results.

Introduction

Glioma is the most common intracranial malignant tumor in the central nervous system (CNS) and has a poor prognosis and high mortality [1]. The incidence of glioma has been sharply increasing worldwide. The statistics of incidence and mortality worldwide for 36 cancers in 185 countries showed that there were 296,851 newly diagnosed cases and 241,037 individuals died from brain and CNS tumor in 2018 [2]. According to the data of National Office for Cancer Prevention and Control in China, the estimated numbers of newly brain and CNS tumor cases and deaths were 101,600 and 61,000, respectively [3]. Despite diagnosis and treatments (surgery, radiotherapy and chemotherapy) have been continuously improving, the outcomes of patients with glioma remain poor. To date, many risk factors have been identified as potential contributors to gliomas risk, such as smoking, ionizing radiation exposure, occupational exposure, environmental carcinogens, higher socioeconomic status and education level [4]. The age, gender, extent of resection, radiotherapy, chemotherapy, and histological grade, tumor size and range have been identified as potential contributors to the prognosis of glioma patients [5, 6]. Moreover, many genetic polymorphisms have been identified to be associated with the susceptibility to gliomas and as well as the prognosis of glioma patients [7–9]. Therefore, it is critical to identify new glioma therapeutic targets and new diagnostic and prognostic biomarkers.

The human plasmacytoma variant translocation 1 (PVT1) gene at the 8q24.21 chromosomal region represents a long non-coding RNA locus that has been identified as a candidate oncogene [10]. Zou et al. found that diffuse glioma patients with high PVT1 expression had poor survival outcome, aberrantly expressed PVT1 could be the independent prognosis biomarkers for glioma patients [11]. The overexpression of PVT1 increased the expression of Atg7 and Beclin1 by targeting miR-186, which induced protective autophagy, thus promoting glioma vascular endothelial cell proliferation, migration, and angiogenesis [12]. Several polymorphisms in PVT1 have been reported to be associated with cancers risk and prognosis. The rs1561927 in PVT1 were found to be associated with poor overall survival in pancreatic ductal adenocarcinoma cases patients [13]. The GG genotype of rs13281615 in PVT1 was associated with increased risk of breast cancer likely by influencing PVT1 expression [14]. The presence of polymorphisms rs13281615 in PVT1 and rs2910164 in miR-146a contribute to a favorable prognosis in colon cancer patients by regulating COX2 expression and cell apoptosis [15].

However, the influence of PVT1 polymorphisms on the risk of glioma as well as the prognosis of glioma patients in the Chinese Han population has not been reported yet. Given the role of PVT1 in tumorigenesis and progression of glioma and prognosis of glioma patients, we hypothesized that the genetic polymorphisms in the PVT1 gene may also influence the risk of glioma and prognosis of glioma patients. To investigate this hypothesis, we recruited 575 patients with glioma and 500 healthy controls to investigate the role of the three SNPs (rs4410871, rs4733789 and rs13255292) in the PVT1 gene in glioma susceptibility and prognosis of glioma patients in the Chinese Han population.

Materials And Methods

Study subjects

We randomly recruited a total of 1075 subjects, including 575 patients with glioma and 500 healthy controls from the department of Neurosurgery at Tangdu Hospital of The Fourth Military Medical University. All patients had newly diagnosed and histologically confirmed glioma by at least 2 senior neuropathologists according to the World Health Organization (WHO) classification in 2007. All controls were selected from the general health examinations in this hospital during the same period. The controls with a history of cancer or brain and central nervous system-related diseases and previously receiving radiotherapy and chemotherapy for certain diseases were excluded. All subjects were unrelated individuals of the Chinese Han.

Follow-up

The clinical follow-up of patients was performed in single-blind fashion with the end point of cardiac death. Patients were followed up through telephone calls outpatient visits, and writing communication with patients or their families by the professional medical staff every month. Overall survival (OS) was measured from the date of diagnosis with glioma to the date of death or last follow-up. Progress free survival (PFS) was calculated from the date of the pathologically confirmed to the progression of the disease, death without progression, or last clinical follow-up.

Demographic and clinical data collection

The demographic and clinical characteristics of patients with glioma were collected and regularly updated from medical records, questionnaires and follow-up, such as age, gender, histology types, tumor grade, surgical methods, extent of resection, treatment with radiotherapy and/or chemotherapy, date of last follow-up, status of patients (living/deceased).

DNA extraction and genotyping

The peripheral blood sample (5 mL) was collected from each patient with glioma and control subject into the ethylene diamine tetra-acetic acid (EDTA)-containing vacutainers and stored at -20 °C until use. We use the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi'an, China) to extract genomic DNA of the samples according to the instructions. We performed a quality analysis of the extracted DNA by measuring its concentration and purity using a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, USA).

The three SNPs (rs4410871, rs4733789 and rs13255292) in PVT1 were selected with minor allele frequency (MAF) > 5% in the global population from the HapMap database. The Agena Bioscience Assay Design Suite V2.0 software (https://agenacx.com/online-tools/) was used to design PCR amplification and extension primers of the three SNPs. The PVT1 polymorphisms were genotyped using the Agena MassARRAY platform with iPLEX gold chemistry (Agena Bioscience, San Diego, CA, USA) according to the protocol described. The Agena Bioscience TYPER software (version 4.0) was used to manage and analyze data.

Bioinformatics analysis

We used the online RegulomeDB software (http://regulome.stanford.edu/) and HaploReg software (http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to predict the possible functional effects on the PVT1 polymorphisms.

Statistical analysis

The basic descriptive statistical analysis of demographic and clinical data was conducted using SPSS 20.0 statistical package (SPSS, Chicago, IL). The Pearson's χ^2 test and Student's t-test were used to analyze the differences in distribution of gender and age between the case and control groups, respectively. The χ^2 test was used to examine whether the genotype frequencies of SNPs among control was consistent with Hardy-Weinberg equilibrium (HWE). The association between PVT1 polymorphisms and glioma risk was assessed under the genetic models by PLINK software (version 1.07). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analysis. Kaplan-Meier method was used to evaluate the survival, and log-rank test to assess the difference between these two groups. Hazard ratio (HR) and 95% CI were calculated from the univariate Cox regression analysis to estimate the association between clinical factors, PVT1 polymorphisms with PFS and OS in glioma patients. Multivariate Cox models were performed to compute HR and 95% CI, after adjustment potential risk factors. All P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Sample characteristics

The basic descriptive statistics for age, gender, WHO classification, WHO grade, surgical methods, chemotherapy, radiotherapy and survival condition were computed and listed in Table 1. There were 575 patients with glioma (320 males and 255 females) and 500 healthy controls (279 males and 221 females) in this case-control study. The mean age of case and control groups was 40.46 years old and 40.53 years old, respectively. The glioma patients consisted of 353 (61.4%) astrocytoma, 36 (6.3%) ependymoma, 36 (6.3%) glioblastoma, 94 (16.3%) oligodendrocytes astrocytoma, 19 (3.3%) oligodendroglioma and 37 (6.4%) other gliomas. There were 369 (64.2%) cases with grade I–II tumors and 206 (35.8%) cases with grade III–IV tumors. 183 (31.8%) patients were treated with STR or NTR; 392 (68.2%) patients were treated with GTR. 364 (63.3%) patients were treated with GK radiotherapy, 155 (27.0%) patients were treated with CRT, and the rest 56 (9.7%) patients did not receive any radiotherapy. 237 (41.2%) patients were treated with chemotherapy (platinum: 118, nimustine: 70, temozolomide: 49, respectively), while 338 (58.8%) patients were not treated. There were 511 (88.9%) deaths, 40 (7.0%) patients survive, and 24 (4.2%) patients are lost to follow-up. No statistically significant differences were found between case and control groups with regarded to age and gender distribution ($p > 0.05$).

Table 1
Characteristics of patients with glioma and controls

Characteristics		Cases (%)	Controls (%)	P
Total		575	500	
Age, Mean ± SD (year)		40.46 ± 18.08	40.53 ± 13.90	0.942
Gender	Male	320 (55.7)	279 (55.8)	0.961
	Female	255 (44.3)	221 (44.2)	
WHO classification	Astrocytoma	353 (61.4)		
	Ependymoma	36 (6.3)		
	Glioblastoma	36 (6.3)		
	Oligodendrocytes astrocytoma	94 (16.3)		
	Oligodendroglioma	19 (3.3)		
	Others	37 (6.4)		
WHO grade	I–II	369 (64.2)		
	III–IV	206 (35.8)		
Surgical method	STR or NTR	183 (31.8)		
	GTR	392 (68.2)		
Chemotherapy	No	338 (58.8)		
	Platinum	118 (20.5)		
	Nimustine	70 (12.2)		
	Temozolomide	49 (8.5)		
Radiotherapy	No	56 (9.7)		
	CRT	155 (27.0)		
	GK	364 (63.3)		
Survival condition	Survival	40 (7.0)		
	Death	511 (88.9)		
	Lost	24 (4.2)		

SD: standard deviation; WHO: World Health Organization; STR: sub-total resection; NTR: near-total resection; GTR: gross-total resection; CRT: conformal radiotherapy; GK: gamma knife

P < 0.05 indicates statistical significance.

PVT1 polymorphisms and glioma risk

This study selected three SNPs in PVT1 which were successfully genotyped (call rate > 95%). The detail information including chromosome id, position, role, allele and potential function predicted, MAF for the SNPs in cases and controls, and HWE of these variants is listed in Table 2. The genotype frequencies of the three SNPs among the controls were in agreement with the HWE ($p > 0.05$). However, three were no significant differences in the allelic frequency distribution of the three SNPs between the case group and the control group ($p > 0.05$). No significant association of the three SNPs in PVT1 with glioma risk.

Table 2

Basic information of PVT1 polymorphisms and association with glioma risk

SNP–ID	Chr	Position	Role	Regulome DB Score	Haploreg	Allele A/B	HWE-P	MAF Case	MAF Control	OR (95% CI)	P
rs4410871	8	127802783	Intron	2b	Promoter histone marks, enhancer histone marks, DNAse, proteins bound, motifs changed, selected eQTL hits	T/C	0.690	0.351	0.339	1.06 (0.88–1.26)	0.550
rs4733789	8	127822157	Intron	5	Promoter histone marks, enhancer histone marks, DNAse, motifs changed	T/C	0.418	0.442	0.451	0.96 (0.81–1.14)	0.667
rs13255292	8	128064327	Intron	4	Enhancer histone marks, DNAse, proteins bound, motifs changed	T/C	0.102	0.198	0.206	0.95 (0.77–1.18)	0.642

SNP: single nucleotide polymorphism; Chr: chromosome; HWE: Hardy–Weinberg equilibrium; Regulome DB Score: 2b: TF binding + any motif + DNase Footprint + DNase peak; 4: TF binding + DNase peak; 5: TF binding or DNase peak; eQTL: expression quantitative trait loci; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval.

P < 0.05 indicates statistical significance.

To further explore the relationship between PVT1 polymorphisms and glioma risk, we performed a genetic model analysis, as shown in Table 3. The results showed that individuals with the TT genotype of rs13255292 was associated with a decreased risk of glioma compared with those with the CC/CT genotype in the recessive model before and after adjusted with age and gender (OR = 0.53, 95% CI: 0.29–0.99, p = 0.046). However, no any significant association was found between the SNPs (rs4410871 and rs4733789) and risk of glioma.

Table 3

PVT1polymorphisms genotypes distribution and association with glioma risk

SNP-ID	Model	Genotype	Case	Control	OR (95%CI)	P	Adjust OR (95%CI)	P
rs4410871	Codominant	CC	249 (43.3)	216 (43.2)	1		1	
		CT	248 (43.1)	229 (45.8)	0.94 (0.73–1.21)	0.632	0.94 (0.73–1.21)	0.636
		TT	78 (13.6)	55 (11.0)	1.23 (0.83–1.82)	0.298	1.23 (0.83–1.82)	0.296
	Dominant	CC	249 (43.3)	216 (43.2)	1		1	
		CT/TT	326 (56.7)	284 (56.8)	1.00 (0.78–1.27)	0.973	1.00 (0.78–1.27)	0.976
	Recessive	CC/CT	497 (86.4)	445 (89.0)	1		1	
		TT	78 (13.6)	55 (11.0)	1.27 (0.88–1.84)	0.203	1.27 (0.88–1.84)	0.202
	Additive				1.06 (0.88–1.26)	0.553	1.06 (0.88–1.26)	0.549
rs4733789	Codominant	CC	179 (31.1)	146 (29.2)	1		1	
		CT	284 (49.4)	257 (51.4)	0.90 (0.68–1.19)	0.461	0.90 (0.68–1.19)	0.46
		TT	112 (19.5)	97 (19.4)	0.94 (0.66–1.34)	0.736	0.94 (0.66–1.34)	0.734
	Dominant	CC	179 (31.1)	146 (29.2)	1		1	
		CT/TT	396 (68.9)	354 (70.8)	0.91 (0.70–1.19)	0.492	0.91 (0.70–1.19)	0.49
	Recessive	CC/CT	463 (80.5)	403 (80.6)	1		1	
		TT	112 (19.5)	97 (19.4)	1.01 (0.74–1.36)	0.974	1.01 (0.74–1.36)	0.976
	Additive				0.96 (0.81–1.14)	0.664	0.96 (0.81–1.14)	0.661
rs13255292	Codominant	CC	364 (63.4)	320 (64.3)	1		1	
		CT	193 (33.6)	151 (30.3)	1.12 (0.87–1.46)	0.381	1.13 (0.87–1.46)	0.378
		TT	17 (3.0)	27 (5.4)	0.55 (0.30–1.03)	0.064	0.55 (0.30–1.04)	0.064
	Dominant	CC	364 (63.4)	320 (64.3)	1		1	
		CT/TT	210 (36.6)	178 (35.7)	1.04 (0.81–1.33)	0.775	1.04 (0.81–1.33)	0.773
	Recessive	CC/CT	557 (97.0)	471 (94.6)	1		1	
		TT	17 (3.0)	27 (5.4)	0.53 (0.29–0.99)	0.046	0.53 (0.29–0.99)	0.046
	Additive				0.95 (0.77–1.18)	0.642	0.95 (0.77–1.18)	0.643

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval.

Adjust OR (95%CI) were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ indicates statistical significance.

In order to reduce the impact of age and gender on the results of statistical analysis, we conducted stratification analysis (Table 4). Our results found that individuals with the TT genotype of rs4410871 was associated with an increased risk of glioma compared with those with the CC genotype in age ≤ 40 years old (OR = 2.05, 95% CI: 1.12–3.75, p = 0.020). Meanwhile, rs4410871 was found to be associated with an increased risk of glioma in the recessive model in age ≤ 40 years old (TT vs. CC/CT: OR = 2.33, 95% CI: 1.31–4.15, p = 0.004).

Table 4

Association of PVT1 polymorphisms with glioma risk stratified by age and gender

SNP_ID	Model	Genotype	Age > 40				Age ≤ 40			
			Case (%)	Control (%)	OR (95% CI)	P	Case (%)	Control (%)	OR (95% CI)	P
rs4410871	Codominant	CC	120 (40.5)	100 (42.6)	1		129 (46.2)	116 (43.8)	1	
		CT	139 (47)	100 (42.6)	1.17 (0.81–1.70)	0.410	109 (39.1)	129 (48.7)	0.77 (0.53–1.11)	0.163
		TT	37 (12.5)	35 (14.9)	0.92 (0.54–1.57)	0.754	41 (14.7)	20 (7.5)	2.05 (1.12–3.75)	0.020
	Dominant	CC	120 (40.5)	100 (42.6)	1		129 (46.2)	116 (43.8)	1	
		CT/TT	176 (59.5)	135 (57.4)	1.11 (0.78–1.57)	0.575	150 (53.8)	149 (56.2)	0.94 (0.66–1.32)	0.705
	Recessive	CC/CT	259 (87.5)	200 (85.1)	1		238 (85.3)	245 (92.5)	1	
		TT	37 (12.5)	35 (14.9)	0.85 (0.51–1.40)	0.511	41 (14.7)	20 (7.5)	2.33 (1.31–4.15)	0.004
	Additive				1.01 (0.79–1.30)	0.941			1.16 (0.89–1.50)	0.270
rs4733789	Codominant	CC	101 (34.1)	65 (27.7)	1		78 (28)	81 (30.6)	1	
		CT	138 (46.6)	124 (52.8)	0.72 (0.48–1.07)	0.100	146 (52.3)	133 (50.2)	1.12 (0.75–1.66)	0.594
		TT	57 (19.3)	46 (19.6)	0.80 (0.48–1.32)	0.378	55 (19.7)	51 (19.2)	1.10 (0.66–1.82)	0.723
	Dominant	CC	101 (34.1)	65 (27.7)	1		78 (28)	81 (30.6)	1	
		CT/TT	195 (65.9)	170 (72.3)	0.74 (0.51–1.08)	0.114	201 (72)	184 (69.4)	1.11 (0.76–1.62)	0.591
	Recessive	CC/CT	239 (80.7)	189 (80.4)	1		224 (80.3)	214 (80.8)	1	
		TT	57 (19.3)	46 (19.6)	0.98 (0.63–1.51)	0.929	55 (19.7)	51 (19.2)	1.02 (0.66–1.58)	0.922
	Additive				0.87 (0.68–1.11)	0.274			1.05 (0.82–1.35)	0.681
rs13255292	Codominant	CC	187 (63.4)	150 (63.8)	1		177 (63.4)	170 (64.6)	1	
		CT	96 (32.5)	73 (31.1)	1.03 (0.71–1.50)	0.881	97 (34.8)	78 (29.7)	1.30 (0.89–1.90)	0.168
		TT	12 (4.1)	12 (5.1)	0.87 (0.38-2.00)	0.737	5 (1.8)	15 (5.7)	0.39 (0.14–1.11)	0.076
	Dominant	CC	187 (63.4)	150 (63.8)	1		177 (63.4)	170 (64.6)	1	
		CT/TT	108 (36.6)	85 (36.2)	1.01 (0.70–1.44)	0.971	102 (36.6)	93 (35.4)	1.16 (0.81–1.67)	0.418
	Recessive	CC/CT	283 (95.9)	223 (94.9)	1		274 (98.2)	248 (94.3)	1	
		TT	12 (4.1)	12 (5.1)	0.86 (0.38–1.96)	0.718	5 (1.8)	15 (5.7)	0.35 (0.12-1.00)	0.050
	Additive				0.99 (0.73–1.33)	0.921			1.00 (0.73–1.36)	0.996
			Male				Female			
rs4410871	Codominant	CC	135 (42.19)	111 (39.78)	1		114 (44.71)	105 (47.51)	1	
		CT	142 (44.38)	130 (46.59)	0.90 (0.64–1.27)	0.547	106 (41.57)	99 (44.8)	0.99 (0.67–1.44)	0.943

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval.

OR (95% CI) were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ indicates statistical significance.

SNP_ID	Model	Genotype	Age > 40				Age ≤ 40			
			Case (%)	Control (%)	OR (95% CI)	P	Case (%)	Control (%)	OR (95% CI)	P
		TT	43 (13.44)	38 (13.62)	0.93 (0.56–1.54)	0.783	35 (13.73)	17 (7.69)	1.90 (1.00-3.59)	0.049
	Dominant	CC	135 (42.19)	111 (39.78)	1		114 (44.71)	105 (47.51)	1	
		CT/TT	185 (57.81)	168 (60.22)	0.91 (0.65–1.26)	0.556	141 (55.29)	116 (52.49)	1.12 (0.78–1.61)	0.540
	Recessive	CC/CT	277 (86.56)	241 (86.38)	1		220 (86.27)	204 (92.31)	1	
		TT	43 (13.44)	38 (13.62)	0.99 (0.62–1.58)	0.952	35 (13.73)	17 (7.69)	1.91 (1.04–3.51)	0.038
	Additive				0.95 (0.75–1.20)	0.651			1.22 (0.93–1.60)	0.151
rs4733789	Codominant	CC	96 (30)	86 (30.82)	1		83 (32.55)	60 (27.15)	1	
		CT	169 (52.81)	144 (51.61)	1.05 (0.73–1.52)	0.790	115 (45.1)	113 (51.13)	0.74 (0.48–1.12)	0.154
		TT	55 (17.19)	49 (17.56)	1.01 (0.62–1.63)	0.982	57 (22.35)	48 (21.72)	0.86 (0.52–1.43)	0.555
	Dominant	CC	96 (30)	86 (30.82)	1		83 (32.55)	60 (27.15)	1	
		CT/TT	224 (70)	193 (69.18)	1.04 (0.73–1.47)	0.828	172 (67.45)	161 (72.85)	0.77 (0.52–1.15)	0.201
	Recessive	CC/CT	265 (82.81)	230 (82.44)	1		198 (77.65)	173 (78.28)	1	
		TT	55 (17.19)	49 (17.56)	0.97 (0.64–1.49)	0.904	57 (22.35)	48 (21.72)	1.04 (0.67–1.60)	0.867
	Additive				1.01 (0.80–1.28)	0.936			0.91 (0.71–1.17)	0.470
rs13255292	Codominant	CC	210 (65.83)	184 (66.19)	1		154 (60.39)	136 (61.82)	1	
		CT	100 (31.35)	76 (27.34)	1.16 (0.81–1.65)	0.431	93 (36.47)	75 (34.09)	1.10 (0.75–1.60)	0.641
		TT	9 (2.82)	18 (6.47)	0.44 (0.19-1.00)	0.051	8 (3.14)	9 (4.09)	0.79 (0.29–2.09)	0.628
	Dominant	CC	210 (65.83)	184 (66.19)	1		154 (60.39)	136 (61.82)	1	
		CT/TT	109 (34.17)	94 (33.81)	1.02 (0.72–1.43)	0.917	101 (39.61)	84 (38.18)	1.06 (0.73–1.54)	0.751
	Recessive	CC/CT	310 (97.18)	260 (93.53)	1		247 (96.86)	211 (95.91)	1	
		TT	9 (2.82)	18 (6.47)	0.42 (0.19–0.95)	0.037	8 (3.14)	9 (4.09)	0.76 (0.29-2.00)	0.578
	Additive				0.91 (0.68–1.20)	0.489			1.02 (0.74–1.40)	0.928

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval.

OR (95% CI) were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ indicates statistical significance.

Gender stratification analysis results showed that rs4410871 was also associated with an increased risk of glioma in female after adjusted with age (TT vs. CC: OR = 1.90, 95% CI: 1.00–3.59, p = 0.049; TT vs. CC/CT: OR = 1.91, 95% CI: 1.04–3.51, p = 0.038). Moreover, rs13255292 was found to be associated with a reduced risk of glioma in the recessive model in male after adjusted with age (TT vs. CC/CT: OR = 0.42, 95% CI: 0.19–0.95, p = 0.037) (Table 4).

Clinical factors and prognosis of glioma patients

We also investigated the impact clinical factors on the OS and PFS of glioma patients (Table 5). The univariate and Cox regression analysis results that the glioma patients with gross-total resection (GTR) was also associated with a reduced risk of death on OS (log-rank p < 0.001, HR = 0.63, 95% CI: 0.52–0.76, p <

0.001) and PFS (log-rank $p < 0.001$, HR = 0.59, 95% CI: 0.49–0.71, $p < 0.001$), compared with the glioma patients with near-total resection (NTR) or sub-total resection (STR). In addition, we also found that the glioma patients with the chemotherapy treatment had a longer OS (log-rank $p < 0.001$) and PFS (log-rank $p = 0.012$), and had a better prognosis of glioma patients (OS: HR = 0.67, 95% CI: 0.56–0.81, $p < 0.001$; PFS: HR = 0.81, 95% CI: 0.67–0.97, $p = 0.025$), compared with the no chemotherapy treatment. The Kaplan Meier survival curve described the survival rates of glioma patients with extent of resection (Fig. 1) and chemotherapy (Fig. 2) treatments, respectively. However, no significant associations were found between the age, gender, WHO grade, radiotherapy and the prognosis of glioma patients as measured by OS and PFS.

Table 5

Univariate analysis of the impact of clinical factors and PVT1 polymorphisms on glioma patient OS and PFS

Variable	Classification	No. of patients/events	OS					No. of patients/events	PFS			
			1 year ST %	MST (month)	Log-rank p	HR (95%CI)	p		1 year ST %	MST (month)	Log-rank p	HR (95
Gender	Male	321/284	32.6	11		1		319/282	20.3	8		1
	Female	257/230	30.7	11	0.352	1.08 (0.91–1.28)	0.394	254/228	15.3	8	0.241	1.1 (0. 1.3
Age(years)	< 40	258/221	35.1	12		1		254/218	20.2	8		1
	≥ 40	320/293	29.1	11	0.061	1.17 (0.98–1.39)	0.086	319/292	16.4	8	0.121	1.1 (0. 1.3
WHO grade	I	371/324	32.8	12		1		369/322	19.1	8		1
	□	207/190	30.0	10	0.094	1.15 (0.96–1.38)	0.125	204/188	16.3	8	0.122	1.1 (0. 1.3
Extent of resection	STR or NTR	184/181	19.6	12		1		181/178	1.70	8		1
	GTR	394/333	37.5	11	< 0.001	0.63 (0.52–0.76)	< 0.001	392/332	25.8	8	< 0.001	0.5 (0. 0.7
Radiotherapy	No	57/46	43.9	12		1		54/43	20.4	10		1
	CRT	156/128	24.0	10				155/127	21.5	8		
	Gamma knife	365/340	33.2	11	0.523	1.07 (0.94–1.22)	0.314	364/340	16.5	8	0.096	1.0 (0. 1.2
Chemotherapy	No	341/319	27.0	9		1		340/318	16.8	7		1
	Yes	237/195	38.7	12	< 0.001	0.67 (0.56–0.81)	< 0.001	233/192	20.1	8	0.012	0.8 (0. 0.9
rs4410871	CC	250/221	34.7	11		1		248/219	18.7	8		1
	CT	250/225	30.8	11		0.98 (0.75–1.29)	0.905	247/223	17.8	8		0.9 (0. 1.2
	TT	78/68	25.6	11	0.809	1.05 (0.87–1.26)	0.611	78/68	17.0	8	0.899	1.0 (0. 1.2
rs4733789	CC	181/163	28.7	11		1		180/162	17.4	8		1
	CT	285/249	33.9	11		0.99 (0.78–1.27)	0.953	282/247	20.4	8		0.9 (0. 1.2
	TT	112/102	31.3	12	0.763	0.94 (0.77–1.15)	0.537	111/101	13.5	8	0.588	0.9 (0. 1.1
rs13255292	CC	365/325	30.4	11		1		361/321	17.7	8		1
	CT	195/171	34.1	12		1.16 (0.71–1.89)	0.555	194/171	18.4	8		1.1 (0. 1.8
	TT	17/17	29.4	10	0.333	0.90 (0.75–1.08)	0.257	17/17	17.6	8	0.407	0.9 (0. 1.0

WHO: World Health Organization; GTR: gross-total resection; NTR: near-total resection; STR: sub-total resection; OS: overall survival; PFS: progression free sur survival rate; MST: median survival time

HR: hazard ratio; 95% CI: 95% confidence interval

P < 0.05 indicates statistical significance.

PVT1 polymorphisms and prognosis of glioma patients

We used the log-rank tests, Cox regression analysis (univariate and multivariate) and Kaplan Meier analysis to evaluate the effect of the four PVT1 polymorphisms on the glioma patients with OS and PFS (Table 5 and Table 6). However, there were no significant associations were found between the polymorphisms of PVT1 and the prognosis of glioma patients.

Table 6
Univariate analysis of the association between and glioma patient OS and PFS

SNP-ID	Genotype	OS		PFS	
		HR (95%CI)	p	HR (95%CI)	p
rs4410871	CC	1		1	
	CT	0.97 (0.73–1.27)	0.800	0.94 (0.71–1.23)	0.642
	TT	1.00 (0.83–1.21)	0.973	0.99 (0.82–1.19)	0.882
rs4733789	CC	1		1	
	CT	1.11 (0.86–1.42)	0.435	1.06 (0.83–1.36)	0.639
	TT	1.08 (0.89–1.32)	0.444	1.05 (0.86–1.29)	0.612
rs13255292	CC	1		1	
	CT	1.01 (0.62–1.65)	0.959	0.96 (0.59–1.56)	0.862
	TT	0.90 (0.75–1.09)	0.277	0.86 (0.71–1.03)	0.099
SNP: single nucleotide polymorphism; OS: overall survival; PFS: progression free survival; HR: hazard ratio; 95% CI: 95% confidence interval					
P < 0.05 indicates statistical significance.					

Discussion

To our knowledge, this case-control study is firstly to investigate the role of PVT1 polymorphisms (rs4410871, rs4733789 and rs13255292) in the susceptibility and survival of glioma in the Chinese Han population. We found that rs13255292 was associated with a decreased risk of glioma in the recessive model in overall or male; rs4410871 was significantly associated with an increased the risk of glioma in age ≤ 40 years old or female. Moreover, the extent of resection and chemotherapy were found to be key prognostic factors in survival of glioma patients. However, no effects were found between PVT1 polymorphisms on prognosis of glioma patients.

PVT1 is one of the transcribed lncRNAs located at the 8q24 human chromosomal region susceptibility locus. LncRNAs are key mediators of pathways involved in tumor suppression and oncogenesis affecting important cellular processes, such as chromatin reprogramming, cis- and trans-regulation of gene expression and mRNA processing [16–18]. PVT1 located downstream of MYC, has been proven to play an important role in cancer, and PVT1 dependence in cancer with MYC copy-number increase [19]. The upregulation of PVT1 has been found to be involved in poor prognosis in colorectal cancer [20], gastric cancer [21], pancreatic cancer [22], glioma [23]. PVT1 modulated GREM1 and BMP downstream signaling proteins through sponging miR-128-3p, thereby promoting tumorigenesis and progression of glioma [24]. The overexpression of PVT1 in glioma tissue and cells and promotes glioma cell proliferation and invasion by targeting miR-200a [25]. PVT1 knockdown could negatively regulate miR-424 to inhibit human glioma cell activity, migration and invasiveness [26].

The rs4410871 and rs13255292 in PVT1 were found to be significantly associated with the risk of glioma in the Chinese Han population. However, no association was found between rs4733789 and glioma risk. These PVT1 polymorphisms have been reported to be associated with disease susceptibility. A Meta-analysis of genome-wide association studies (GWAS) identified that rs4410871 influenced allergic sensitization [27]. The rs4410871 was found to be associated with susceptibility to multiple sclerosis [28, 29]. Previous meta-analysis of GWAS identified that rs4733789 was associated with adult height in an East Asian population [30]. The men with the minor allele T in rs4476972 and with the major allele C in rs4733789 tend to have a lower risk of developing prostate cancer in African Americans population [31]. A GWAS and a pooled study of three Eastern Asian populations observed a significant association between rs13255292 (PVT1) and diffuse large B-cell lymphoma risk [32, 33]. The rs13255292 was also found to be associated with ovarian cancer [34]. However, this study was firstly to investigate the association between the three PVT1 polymorphisms and glioma risk. Therefore, the results need to be confirmed in multi-ethnic population with larger scale.

This study also explored the impact of clinical features and PVT1 polymorphisms on the prognosis of glioma patients. Our results found that extent of resection and chemotherapy were key prognostic factors in survival of glioma patients. However, gender, age, who grade, radiotherapy, and PVT1 polymorphisms have no effects on survival of glioma patients. Wang et al. indicated that degree of resection and pathological grade were independent prognostic factors for patients with malignant gliomas, but age and gender have no effect on glioma survival outcome [35]. The extent of resection and sex was found to be as prognostic factors for overall survival in pediatric high-grade glioma [36]. This comprehensive analysis of multicentric glioma patients revealed that age > 54 years old, surgical resection, and radiotherapy were significantly associated with improved survival and were independent prognostic factors for OS. Radiotherapy and radiotherapy combined with chemotherapy were independent prognostic factors for surgical patients' OS as well [37]. There

are many reasons for conflicting results, such as differences in sample size, ethnicity, tumor grade, and experiment method. Therefore, further study is needed to confirm the results.

There were several limitations in the present study. First, only three SNPs in PVT1 were selected in this study which may not represent a comprehensive view of PVT1 variation. Further studies on variation in susceptible regions of PVT1 are needed. Second, data were not available for some risk factors (e.g., cigarette smoking, alcohol consumption), therefore, these factors should be taken into account in future studies. Third, since this is a very preliminary study, further functional studies are also required to explore the mechanisms of the PVT1 polymorphisms affected the risk and prognosis in glioma patient.

Conclusions

In conclusion, the results indicated that PVT1 polymorphisms (rs13255292 and rs4410871) were significantly associated with the risk of glioma. The extent of resection and chemotherapy were found to be key prognostic factors in survival of glioma patients. However, the PVT1 polymorphisms have no effects on prognosis of glioma patients. Further study with large samples on the role of PVT1 polymorphisms in the susceptibility and survival of glioma is warranted to obtain more conclusive outcomes.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee of the Tangdu Hospital of The Fourth Military Medical University, and was conducted in accordance with the principles of the Declaration of Helsinki. Blood samples and signed informed consent forms were obtained from enrolled individuals prior to their participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interest exists.

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None.

Authors' contributions

Ya Gao participated in the study design; Xiaoying Ding drafted the manuscript; Yaqin Zhao was involved with the analysis of data; Haozheng Yuan and Yong Zhang performed the experiments. All authors have read and approved the final manuscript.

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Figures

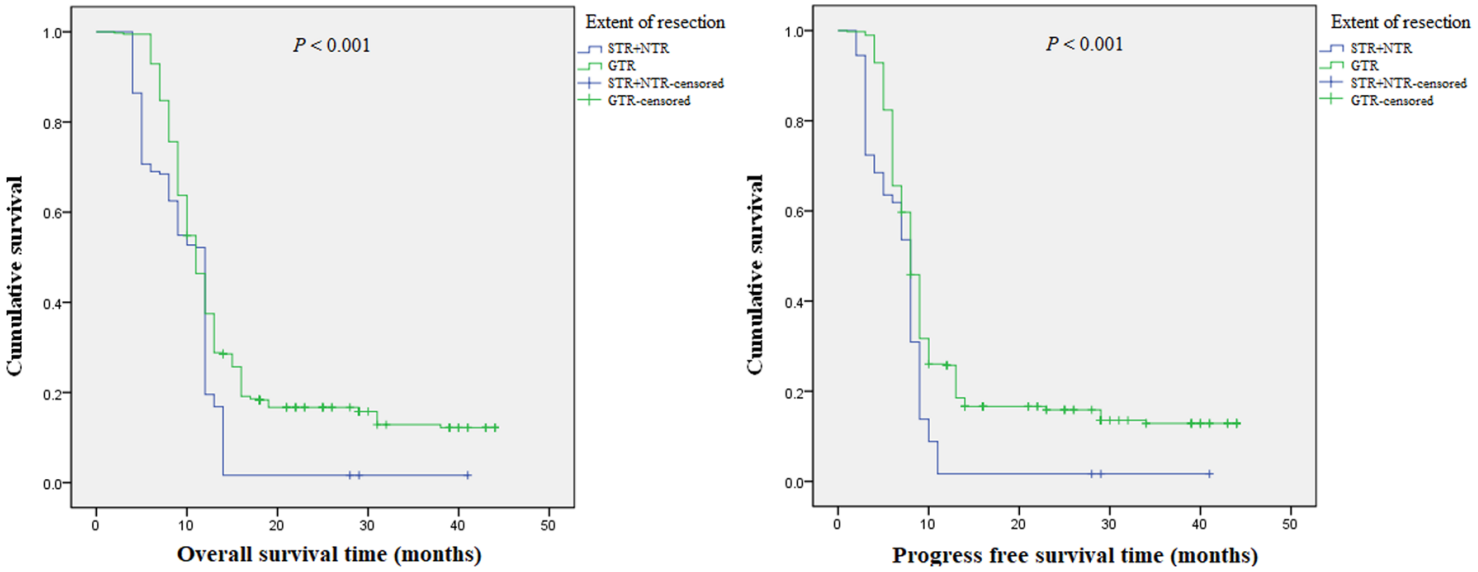

Figure 1

Kaplan–Meier curves for overall survival and progression-free survival of extent of resection in glioma patients

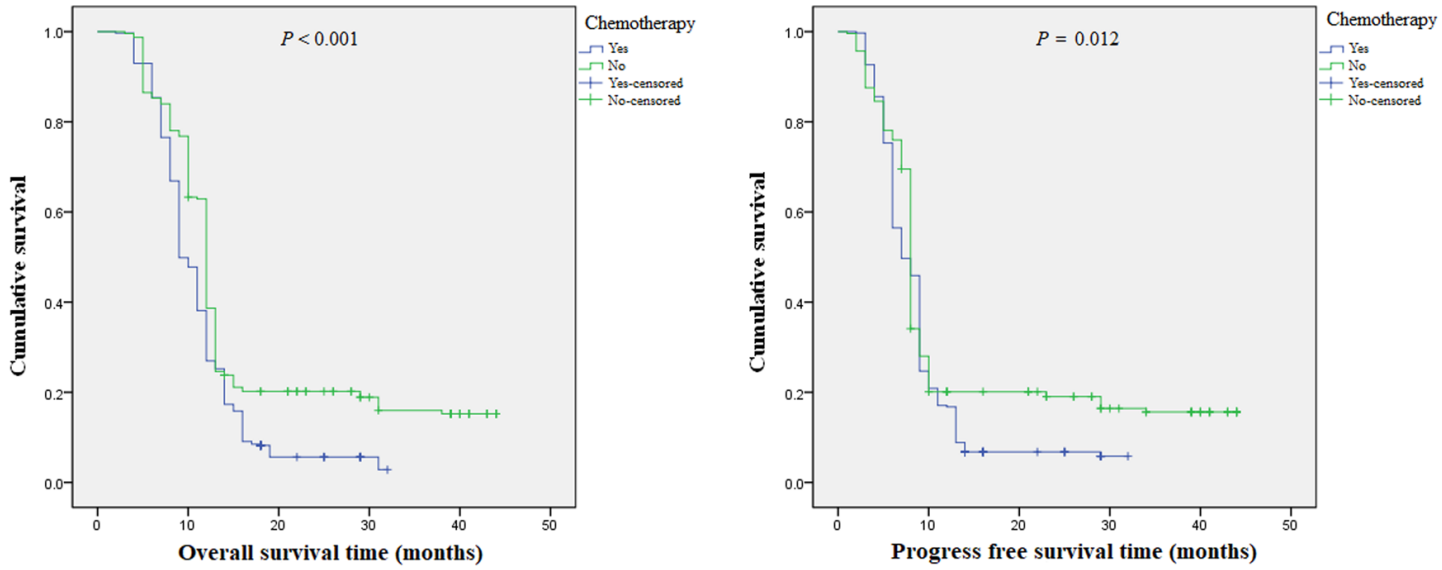

Figure 2

Kaplan–Meier curves for overall survival and progression-free survival of chemotherapy in glioma patients