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Association between RTEL1, PHLDB1, and TREH Polymorphisms and Glioblastoma Risk: A Case-Control Study

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Statistical Analysis C
Data Interpretation D
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Background: Glioblastoma (GBM) is a highly invasive, aggressive, and incurable brain tumor. Genetic factors play important roles in GBM risk. The aim of this study was to elucidate the influence of gene polymorphism on GBM susceptibility.

Material/Methods: In this case-control study, we included 72 GBM patients and 320 healthy controls to analyze the association between 29 single-nucleotide polymorphisms and GBM cancer risk in the Chinese Han population. The single-nucleotide polymorphisms were determined by Sequenom MassARRAY RS1000 and statistical analysis was performed using SPSS software and SNPStats software.

Results: Using the χ^2 test, we found that rs2297440 and rs6010620 in *RTEL1* increased risk of GBM. In the recessive model, we also found that the genotypes "CC" of rs2297440 and "GG" of rs6010620 in *RTEL1* significantly increased GBM risk. The variant TT genotype of *TREH* rs17748 and the variant TT genotype of *PHLDB1* rs498872 decreased GBM risk in the recessive model. We also found that the *TREH* rs17748 variant C allele showed an increased risk in males in the dominant model.

Conclusions: Our results suggest a significant association between the *RETL1*, *TREH*, and *PHLDB1* genes and GBM development in the Han Chinese population.

MeSH Keywords: Case-Control Studies • Glioblastoma • Polymorphism, Single Nucleotide

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Background

According to the World Health Organization (WHO) classification of tumors, a grading scheme, which represents a malignancy scale and a key factor influencing the choice of therapies, has been successfully applied to astrocytomas, the most common type of glioma. The WHO defines glioblastoma as grade IV, the most malignant grade [1]. Glioblastoma is the most frequent type of brain tumor and the median survival time is 2 years after diagnosis [1,2]. At present, no effective treatment has been developed for glioblastoma patients.

Molecular epidemiology focuses on the use of biomarkers in epidemiologic research. Molecular biomarkers are typically indicators of exposure, effect, or susceptibility [3]. Known risk factors, high-dose ionizing radiation, and smoking, account for only a small proportion of cases. Recently, genome-wide association studies determined that inherited variants in some chromosomal regions, such as chromosomes 20q13.3, 5p15.3, and 11q23.3, have a significant association with the risk of glioma [4,5].

Although genome-wide association studies (GWAS) found that some sites have relationships with glioma, these studies are mainly limited to the European populations [4,5] and there were significant differences between Europeans and Chinese in genetic background. Therefore, we investigated whether the gene polymorphisms contribute to glioblastoma risk in a Chinese Han population from northwestern China.

Material and Methods

Study participants

From October 2011 to September 2012 we recruited 72 GBM patients into an on-going molecular epidemiological study at the Department of Neurosurgery of the Tangdu Hospital affiliated with The Fourth Military Medical University in Xi'an, China. The patients were newly diagnosed and histologically confirmed. Tumor histological type and grade were determined based on the WHO criteria and we successfully genotyped 72 GBM cases for further study.

As controls we randomly selected 320 unrelated healthy individuals from the medical center of Tangdu Hospital from June 2011 to July 2012 according to standard recruitment and exclusion criteria. Detailed recruitment and exclusion criteria were used. Subjects with chronic diseases and conditions involving vital organs such as the heart, lung, liver, kidney, and brain, and/or had severe endocrinological, metabolic, or nutritional diseases were excluded from this study. All of the control subjects were generally healthy without diseases related to the vital organs and serum levels of alpha-fetoprotein and plasma carcinoembryonic antigen were within normal range. We excluded 18 samples because of missing information, resulting in successful genotyping of 302 healthy control subjects. All enrolled subjects were Chinese Han ethnicity genetically from Xi'an and the surrounding areas.

We obtained demographic and personal data through a face-to-face interview via a standardized epidemiological questionnaire, which including age, sex, ethnicity, residence, smoking status, alcohol drinking, education status, and family history of cancer. In addition, patient clinical information was obtained through a medical record review or consulting treating physicians to understand the patient's condition.

The use of human blood sample and the protocol in this study strictly conformed to the principles expressed in the Declaration of Helsinki and were approved by the institutional ethics committees of Tangdu Hospital and Northwest University. Written informed consent was obtained from all participants before their participation in the study.

SNP selection and genotyping

According to the previous glioma association analysis and SNPs with minor allele frequency (MAF) greater than 0.05 in the HapMap CHB (Han Chinese in Beijing, China) population, we picked 29 SNPs from 21 genes. In genome-wide association studies, the smaller MAF will decrease statistical power, resulting in false-negative results. If the MAF <5%, some *loci* variants could not be detected in the samples, so the SNPs with minor allele frequency (MAF) greater than 0.05 were used. We isolated genomic DNA samples from the whole blood with GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xian City, China), and concentrations were measured using a NanoDrop 2000 device (Thermo Scientific, Waltham, Massachusetts, USA). MassARRAY Assay Design 3.0 Software (Sequenom, San Diego, CA, USA) was used to design the PCR assay and iPLEX single-base extension primers for the Multiplexed SNP MassEXTEND assay [6]. The SNP genotypes were obtained according to the iPLEX protocol provided by Sequenom MassARRAY RS1000 (Sequenom. San Diego, California, USA) and the Sequenom Typer 4.0 software was used for data analysis [6,7].

Statistical analysis

SPSS 16.0 software (SPSS, Inc.) was used for statistical analyses. The chi-squared test was used to compare the differences in frequency distributions of genotypes and alleles between cases and controls [8]. Hardy-Weinberg equilibrium was assessed using a Pearson chi-squared test only among controls at the 1% level. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) were obtained by binary logistic regression analysis, which adjusted for age and sex [9]. The most

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common genotype in the controls was used as the reference group. The possibility of sex differences was evaluated by a genotype test for each tSNP in males and females separately. We adopted the SNP stats (website software from *http://bioinfo.iconcologia.net/snpstats/start.htm*) to analyze the association of certain single-nucleotide polymorphism *loci* contributed to the glioblastoma risk under variant models [10]. We used the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) to select the best-fit model for each SNP. All *p* values presented were calculated based on a 2-sided test, and $p<0.05$ was considered significant.

Results

Table 1 shows the basic information of candidate SNPs in our study such as chromosome position and minor allele frequency in case and control groups. All *loci* meet the Hardy-Weinberg equilibrium at the 1% level. We used the chi-squared test to assess the influence of gene polymorphism of GBM risk in the allele model, and found that 2 SNPs significantly increased GBM risk: rs2297440 [*RTEL1* (regulator of telomere elongation helicase 1; OMIM 608833), OR=1.72, 95% CI: 1.17–2.52, $p<0.01$] and rs6010620 [*RTEL1*, OR=1.72, 95% CI: 1.18–2.52, $p<0.01$)] (Table 1).

Genetic model analysis found that the variant genotype "TT" of rs17748 in *TREH* (a, a-trehalose-1-d-glucohydrolase; trehalase) – *PHLDB1* (pleckstrin homology-like domain, family B, member 1) decreased the risk of GBM in the recessive model (OR=0.24, 95% CI: 0.06-1.05, $p=0.02$) (Table 2). The variant genotype "TT" of rs498872 in *PHLDB1* also correlated with a decreased risk in the recessive model (OR=0.14, 95% CI: 0.02–1.09, $p=0.01$) (Table 2). Conversely, individuals carrying the variant CC genotype of rs2297440 in *RTEL1* had higher GBM risk than those carrying TT and TC genotype in the recessive model (OR=7.46, 95% CI: 2.91–19.12, $p<0.01$). The genotype "GG" of rs6010620 in *RTEL1* also showed an increased risk in the recessive model (OR=7.72, 95% CI: 3.06–19.51, $p<0.01$) (Table 2).

We further sought to determine whether any of the 29 SNPs had a sex-specific effect on GBM risk, and found that allele "C" of rs17748 in *TREH* increased GBM risk in males (OR=4.10, 95% CI: 1.96–8.59, $p=0.04$) in the dominant model (Table 3).

Discussion

In this case-control study we genotyped 29 SNPs in the Han Chinese population and identified *RTEL1*rs2297440 and rs6010620, *TREH*rs17748 and *PHLDB1* rs498872 are potentially associated with GBM. We also found that the allele "C" of rs17748 in the *TREH* gene showed an increased risk in males in the dominant model.

The *RTEL1* gene is located in 20q13.33. *RTEL1* encodes a DNA helicase [11] that plays a crucial role in regulating telomere length in mice [12]. Telomere maintenance and DNA repair are essential processes for preventing genome instability and cancer [13]. Loss of *RTEL1* induces shortened telomere length, chromosome breaks, and translocations [12]. Based on these observations, *RTEL1* dysfunction appears to be closely related to the incidence of cancer. Moreover, *RTEL1* plays an important role in maintaining genomic stability by suppressing homologous recombination [13] and is a key protein in the repair of double-strand breaks (DSBs) through direct involvement in the DSB repair (DSBR) pathway. DSBR plays a prominent role in cell survival, maintenance of genomic integrity, and prevention of tumorigenesis [14,15].

Our results suggest that polymorphisms of the *RTEL1* gene may influence the risk of GBM in the Han Chinese population. Moreover, genome-wide association studies have shown that rs6010620 and rs2297440 in 20q13.33 (*RTEL1*) are related to glioma risk in the European population [4]. Wrensch et al. [16] reported that rs6010620 is associated with susceptibility to high-grade glioma, and Egan et al. [17] showed that SNPs of *RTEL1* are associated with both low- and high-grade astrocytic tumors. Thus, *RTEL1* may play complex roles in the development of gliomas of different origins [18].

rs498872 maps to the 5' untranslated region of the *PHLDB1* gene at 11q23.3. 20 *PHLDB1* was expressed in all tissues examined, with the highest expression in ovary, brain, lung, and kidney. *PHLDB1* protein contains an N-terminal phosphorylation-dependent forkhead-associated protein interaction domain, a central chromosome segregation ATPase domain, and a C-terminal pleckstrin homology (PH) domain [19]. Studies have shown that the PH domain can bind PI(3,4,5)P3 and that *PHLDB1* functions in adipocytes as a positive regulator of Akt activation, where it is required for optimal insulin-induced glucose transport and GLUT4 translocation [20]. It has been reported that PHLDB1 is an insulin-responsive protein and enhances Akt activation. However, there are few studies of its potential regulatory or growth promoting activities with respect to glioma genesis. This SNP was also reported to be associated with a change in diastolic blood pressure [21]. In our study, we also found that *PHLDB1* rs498872 is associated with GBM in the Han Chinese population. In support of this, association between glioma risk and rs498872 was recently identified in a genome-wide association study [4]. This association was confirmed in other studies, including a previous study in a Chinese Han population [22–24]. Therefore, although *PHLDB1* is associated with low-grade glioma, there is currently no direct functional evidence for a role of *PHLDB1* in initiation of GBM.

SNPrs17748 is located downstream of *TREH* and the 3'UTR region of the *PHLDB1* gene. *TREH* is located on chromosome 11q23 and encodes hydrolyses trehalose enzyme [25]. Trehalose

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Table 1. Basic information on candidate tSNPs analyzed in this study.

SNP ID	Gene	Position	Band	Base change	Role	MAF case	MAF control	p^a value for HWE test	OR 95%CI	p^b value
rs498872	PHLDB1	118477367	11q23.3	C/T	Downstream	0.264	0.276	0.80	0.94 (0.62–1.42)	0.76
rs980444	PLA2G4A	38167710	15q14	T/C		0.417	0.443	0.99	0.90 (0.62–1.30)	0.57
rs12439272	PLCB2	40584804	15q15.1	G/A	Intron	0.118	0.086	0.76	1.43 (0.80–2.55)	0.23
rs7003908	PRKDC	48770702	8q11.21	A/C	Intron	0.243	0.226	0.62	1.10 (0.72–1.68)	0.66
rs701848	PTEN	89726745	10q23.31	T/C	3' UTR	0.444	0.409	0.91	1.16 (0.80–1.67)	0.44
rs2160138	RPA3	7755797	7p21.3	T/C	Intron	0.243	0.214	0.41	1.18 (0.77–1.81)	0.44
rs4140805	RPA3	7727101	7p21.3	T/G	Intron	0.229	0.208	0.42	1.13 (0.73–1.75)	0.57
rs6947203	RPA3	7737048	7p21.3	C/T	Intron	0.139	0.133	0.79	1.06 (0.62–1.79)	0.84
rs2297440	RTEL1	62312299	20q13.33	T/C	Intron	0.375	0.259	0.05	1.72 (1.17–2.52)	<0.01*
rs4809324	RTEL1	62318220	20q13.33	T/C	Intron	0.097	0.113	0.72	0.85 (0.46–1.55)	0.59
rs6010620	RTEL1	62309839	20q13.33	A/G	Intron	0.382	0.264	0.03	1.72 (1.18–2.52)	<0.01*
rs2072532	SLC8A1	40366301	2p22.1	T/C	Intron	0.167	0.205	1.00	0.78 (0.48–1.25)	0.3
rs2110922	SLC8A1	40363644	2p22.1	T/G	Intron	0.403	0.43	1.00	0.89 (0.62–1.29)	0.55
rs202445	SOD1	33025667	21q22.11	A/G	Promoter	0.021	0.012	0.99	1.80 (0.46–7.06)	0.65
rs2066804	STAT1/ STAT4	191841759	2q32.2	C/T	Intron (boundary)	0.5	0.448	0.77	1.23 (0.86–1.77)	0.26
rs2853676	TERT	1288547	5p15.33	G/A	Intron	0.222	0.171	0.06	1.39 (0.89–2.17)	0.15
rs3755377	TGFA	70732852	2p13.3	C/T	Intron	0.417	0.457	0.21	0.85 (0.59–1.23)	0.38
rs1805015	IL4R	27374180	16p12.1	T/C	Coding exon	0.104	0.098	0.56	1.07 (0.59–1.95)	0.82
rs7989882	TNFRSF19	24214603	13q12.12	G/A	Intron	0.229	0.236	0.85	0.96 (0.63–1.48)	0.86
rs1042522	TP53	7579472	17p13.1	G/C	Coding exon	0.486	0.409	0.83	1.37 (0.95–1.97)	0.09
rs8079544	TP53	7580052	17p13.1	C/T	Intron	0.118	0.084	0.42	1.45 (0.81–2.60)	0.21
rs17748	TREH, PHLDB1	118528424	11q23.3	C/T	Downstream	0.229	0.271	0.14	0.80 (0.52–1.23)	0.31
rs3828550	KDR	55976451	4q12	C/T	Intron	0.299	0.318	0.49	0.91 (0.61–1.36)	0.65
rs861530	XRCC3	104174123	14q32.33	A/G	Intron	0.41	0.42	0.99	0.96 (0.66–1.39)	0.82
rs3212092	XRCC3	104168644	14q32.33	C/T	Intron	0.063	0.04	0.83	1.61 (0.73–3.55)	0.23
rs1056503	XRCC4	82648977	5q14.2	G/T	Coding exon	0.264	0.284	0.99	0.90 (0.60–1.36)	0.63
rs3770502	XRCC5	217045059	2q35	G/A	Intron	0.132	0.166	0.95	0.76 (0.45–1.29)	0.31
rs9288516	XRCC5	217053264	2q35	T/A	Intron	0.403	0.458	0.60	0.80 (0.55–1.15)	0.23
rs6519265	XRCC6	42025350	22q13.2	G/A	Intron	0.125	0.084	0.17	1.55 (0.88–2.74)	0.13

MAF – minor allele frequency; OR – odds ratio; 95% CI – 95% confidence interval. p^a<0.01 indicates statistical significance; p^b<0.05 indicates statistical significance for allele model.

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Table 2. Single-SNP analysis in different genetic models.

Model	rs17748			rs498872			rs2297440			rs6010620		
	Genotype	OR (95% CI)	*p*-value	Genotype	OR (95% CI)	*p*-value	Genotype	OR (95% CI)	*p*-value	Genotype	OR (95% CI)	*p*-value
Codominant	C/C	1	0.07	C/C	1	0.02	T/T	1	<0.01*	A/A	1	<0.01*
	C/T	1.13 (0.65–1.96)		C/T	1.40 (0.82–2.40)		T/C	1.22 (0.69–2.16)		G/A	1.13 (0.64–2.01)	
	T/T	0.25 (0.06–1.12)		T/T	0.17 (0.02–1.30)		C/C	8.24 (3.07–22.10)		G/G	8.22 (3.11–21.72)	
Dominant	C/C	1	0.77	C/C	1	0.55	T/T	1	0.08	A/A	1	0.11
	C/T-T/T	0.92 (0.54–1.57)		C/T-T/T	1.18 (0.69–1.99)		T/C-C/C	1.61 (0.94–2.75)		G/A-G/G	1.54 (0.90–2.63)	
Recessive	C/C-C/T	1	0.02*	C/C-C/T	1	0.01*	T/T-T/C	1	<0.01*	A/A-G/A	1	<0.01*
	T/T	0.24 (0.06–1.05)		T/T	0.14 (0.02–1.09)		C/C	7.46 (2.91–19.12)		G/G	7.72 (3.06–19.51)	
Overdominant	C/C-T/T	1	0.37	C/C-T/T	1	0.09	T/T-C/C	1	0.69	A/A-G/G	1	0.47
	C/T	1.28 (0.75–2.21)		C/T	1.60 (0.94–2.71)		T/C	0.90 (0.53–1.53)		G/A	0.82 (0.48–1.41)	

* $p<0.05$ indicates statistical significance.

Table 3. Association between covariate sex and the risk of GBM for rs17748 in the dominant model.

Genotype	Gender	Control	Case	OR (95% CI)
C/C	Female	108	13	1.00
	Male	59	28	4.10 (1.96–8.59)
C/T-T/T	Female	73	15	1.00
	Male	59	16	1.35 (0.61–2.97)

Test for interaction in the trend: 0.04. * $p<0.05$ indicates statistical significance.

is an non-reducing disaccharide that hydrolyzes trehalose to 2 glucose molecules [26]. Research on the properties of renal and urinary human trehalase found that expression of trehalase increased damage to renal tubes. Therefore, it is a useful marker of renal proximal tubular damage [27]. To the best of our knowledge, the present study is the first to show a relationship between *TREH* rs17748 and GBM susceptibility. However, the *TREH* function needs further study.

Conclusions

Our findings and those of previous studies suggest that polymorphisms of particular genes play a role in GBM development. These findings should be taken into consideration in future research of genes causing disease susceptibility. Due to the low incidence, the sample size was insufficient. Based on the limitation of the present study, larger-sample studies are warranted to confirm our findings. The exact functions of these genes in GBM and the regulatory mechanisms for gene expression have not been elucidated and need to be further investigated.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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