

Impact of *TREM1* Variants on the Risk and Prognosis of Glioma in the Chinese Han Population

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Background: Glioma is the main pathological subtype of brain tumors with high mortality.

Objective: This study aimed to elucidate the correlation between *TREM1* variants and glioma risk in the Chinese Han population.

Methods: Genotyping of six variants of *TREM1* was completed by Agena MassARRAY platform in 1061 subjects (503 controls and 558 glioma patients). The relationship between *TREM1* polymorphisms and glioma risk was calculated using the logistic regression model, with odds ratio (OR) and 95% confidence intervals (CIs). A multifactor dimensionality reduction (MDR) method was performed to assess SNP-SNP interactions to predict glioma risk.

Results: In this research, overall analysis illustrated an association between *TREM1* rs9369269 and an increased risk of glioma. Rs9369269 was also related to the risk of glioma in patients aged ≤40 years and females. Subjects with rs9369269 AC genotype were likely to obtain glioma compared to people with CC genotype (patients with astrogloma vs healthy people). Compared to TT genotype carriers, carriers with AT genotype of rs1351835 were significantly associated with overall survival (OS).

Conclusion: Taken together, the study identified the association between *TREM1* variants and glioma risk and *TREM1* variants were significantly associated with the prognosis of glioma. In the future, larger samples are needed to verify the results.

Keywords: glioma, *TREM1*, single nucleotide polymorphisms, risk

Introduction

Glioma, originated from glial or precursor cells, is the main pathological subtype of brain tumors, taking up about 80% of primary malignant brain tumors in human.¹ Gliomas include astrocytoma, oligodendroglioma and ependymoma.² According to their clinicopathological features, gliomas can be divided into grades I-IV, thereinto, grade IV glioma is also called glioblastoma multiforme. Despite great advances in glioma diagnosis, the number of gliomas remains increasing. In 2015, it was reported that 1,016,000 cases of brain and central nervous system (CNS) tumor were newly diagnosed in China, and the incidence rate in males was slightly higher than that in females.³ At present, surgery is the main treatment for glioma, and there are various treatments, such as chemotherapy, radiotherapy and immunotherapy. However, malignant brain tumors remain difficult to treat, and the overall survival rate (OS) was low.² Therefore, it is urgent to study the pathogenesis of glioma. In recent years, some studies have shown that genetic factors were correlated with the risk and prognosis of glioma.^{4,5} The effect of genetic variants in glioma risk has attracted high attention, revealing that single nucleotide polymorphisms (SNPs) in cancer-related genes, such as *TREH*, *IL4R*, *CCDC26*, *RTEL1*, *TERT*, etc., were linked to the risk and prognosis of glioma.⁶⁻⁸

Triggering receptor expressed on myeloid cells 1 (*TREM1*) was a recently discovered cell surface receptor expressed on neutrophils and monocytes.⁹ As a member of the immunoglobulin superfamily, it can trigger the release of pro-inflammatory chemokines and cytokines (interleukin-8, tumor necrosis factor α and interleukin-1)^{10,11} and activate downstream signaling pathways by interacting with DAP12. In an article reported by Wu et al,¹² loss of *TREM1* attenuated hepatocellular carcinoma induced by diethylnitrosamine (DEN). When deletion is complemented, the development of hepatocellular carcinoma is

exacerbated. Thus, *TREM1* was a key determinant of hepatocellular carcinoma. Yang et al have also found that *TREM1* level was increased under anoxic conditions and were associated with a marker of THP1-induced macrophage M2 polarization in glioblastoma cell line.¹³ *TREM1* downregulation can reduce the migration and vascular morphology in glioblastoma cells. In vivo, it can inhibit tumor growth, probably by reducing the release of CSF1 cytokine.¹³ Therefore, *TREM1* played a critical role in the development of glioma. SNPs have also been reported to be associated with the occurrence of diseases. For example, rs4711668 polymorphism in *TREM1* gene was significantly associated with severe coronary atherosclerosis in Russian population.¹⁴ *TREM1* rs2234237 was associated with malaria susceptibility in Colombian populations.¹⁵ However, no studies illustrated the association between *TREM1* SNPs and glioma susceptibility.

In this study, based on the Agena MassARRAY platform, the association between polymorphisms of *TREM1* and the risk of glioma was assessed in the Chinese population by logistic regression analysis, providing the theoretical basis for elucidating the mechanism of *TREM1* in glioma.

Materials and Methods

Study Population

On the basis of G*Power (3.1.9.7) software, 1061 subjects (503 controls and 558 glioma patients) were randomly recruited from Xi'an Chang'an District Hospital. All glioma patients were confirmed by imaging and histopathological examination. The clinical information about glioma patients was collected by professionals, which included age, gender, surgical method, chemotherapy and radiotherapy regimen, the date of the last follow-up and the patient's survival at the last follow-up. People with a history of cancer or brain and CNS diseases were excluded from the control group. The study was approved by the ethics committee of Xi'an Chang'an District Hospital and Northwest University and followed the Declaration of Helsinki. Each participant was informed of the purpose of this study and signed written informed consent.

SNP Selection and Genotyping

Based on the 1000 Genomes Project data, SNPs in *TREM1* with minor allele frequency (MAF) >5%, Hardy-Weinberg equilibrium (HWE) >0.01 and $r^2 > 0.8$ were selected from the global population. Blood samples (5mL) extracted from all participants were collected in EDTA-containing vacutainers, and gDNA was subsequently extracted by the GoldMag whole-blood genomic DNA purification kit (GoldMag Co. Ltd., Xi'an, China) to be the amplification template. MassARRAY iPLEX Gold Assay (Agena Bioscience, San Diego, CA, USA) was used for the genotyping of *TREM1* polymorphisms. Also, the primers for amplification and extension were designed using the Agena MassARRAY Assay Design software, version 3.0 and remove the ineffective primers and nonspecific primers, and the sites with call rate greater than 95% were retained. The PCR reaction consisted of 1μL of 10ng/μL gDNA and 4μL of PCR mixture that contained 1.8μL of water, 0.5μL of 10×PCR buffer, 0.4μL of 25mM MgCl₂, 0.1μL of 25mM dNTP, 1μL of PCR primer mix and 0.2μL of 5U/μL PCR Taq (Agena Bioscience, Inc., USA). The PCR conditions were as follows: initial denaturing at 95°C for 2 min, followed by 45 cycles of denaturing at 95°C for 30 s, annealing at 56°C for 30 s, and final extension at 72°C for 60 s. Then, the final step was to keep it at 25°C indefinitely. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry was used to identify SNP alleles of different quality extension primers after alkaline phosphatase reaction, single group extension and resin desalination reaction. Finally, six SNPs (rs9369269, rs4714447, rs2170887, rs2234242, rs1351835 and rs2234237) were selected, and the information of PCR primers are shown in [Supplementary Table 1](#). The MassARRAY Typer 4.0 software was used to perform data processing.

Statistical Analysis

Independent sample *t*-test and Pearson's Chi-squared test were used to assess differences in the information of study subjects (age, gender, etc.). The genotype frequencies distribution of selected SNPs in the control group was evaluated by Pearson's Chi-squared test to determine whether they were consistent with HWE. The distribution of allele frequencies of selected SNPs between cases and controls were also compared by Pearson's Chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association between polymorphisms of *TREM1* and glioma risk using logistic regression analysis. Codominant, dominant, recessive, and log-additive models were used for testing the

relationship between *TREM1* SNPs and glioma risk, as shown by PLINK software. In addition, using a bioinformatics database,^{16,17} we examined the expression level and prognosis of *TREM1* in glioma patients. We also performed multivariate analyses of associations among genotypes, various factors, overall survival (OS) and progression-free survival (PFS), with hazard ratios (HRs) and 95% CIs. Multifactor dimensionality reduction (MDR) was conducted to assess SNP–SNP interactions in glioma risk assessment. All statistical analyses were calculated with SPSS software, version 27.0, and Excel software, version 22.0. $p < 0.05$ was considered statistically significant.

Results

Study Subjects and Selected SNPs

This study included 503 controls and 558 glioma patients. The average ages of the two groups ($p = 0.815$) were 40.75 ± 13.99 years and 40.52 ± 18.08 years, respectively, and no age-related difference was observed. In addition, there was no gender difference between the two groups ($p = 0.832$). The clinical information about participants is shown in Table 1. Table 2 listed the information about the selected SNPs (rs9369269, rs4714447, rs2170887, rs2234242, rs1351835 and rs2234237) in *TREM1*. All SNPs were in accordance with HWE ($p > 0.05$).

The Correlation Between *TREM1* Polymorphisms and Glioma Susceptibility

Multiple model analysis for the association between *TREM1* polymorphisms and glioma risk is presented in Table 3 and Figure 1. The results showed a relationship between rs9369269 AC genotype and an increased glioma risk in the codominant model (OR = 1.46, 95% CI: 1.08–1.97, $p = 0.014$), and there was a correlation between C/C-A/C genotype of rs9369269 and an increased glioma risk in the dominant model, compared to the A/A genotype (OR = 1.44, 95% CI: 1.08–1.91, $p = 0.013$).

Table 1 Demographic and Clinical Information About Participants

Variants	Overall Survival				Progression-Free Survival			
	Total	Event	χ^2	Log-Rank p -value	Total	Event	χ^2	Log-Rank p -value
Gender								
Male	307	273	1.014	0.314	305	271	1.541	0.214
Female	251	226			248	224		
Age								
<40 years old	248	214	3.559	0.059	244	211	2.714	0.100
≥40 years old	310	285			309	284		
WHO grade								
I–II	352	310	1.201	0.273	350	308	1.214	0.271
III–IV	206	189			203	187		
Operation								
NTR/STR	175	173	28.734	$p < 0.001$	172	170	36.086	$p < 0.001$
GTR	383	326			381	325		
Radiotherapy								
No	57	46	2.121	0.346	54	43	5.588	0.061
Conformal radiotherapy	145	119			144	118		
Gamma knife	356	334			355	334		
Chemotherapy								
No	331	309	17.541	$p < 0.001$	330	308	3.699	0.054
Yes	227	190			223	187		
Progress								
No	31	0	104.726	$p < 0.001$	31	0	104.503	$p < 0.001$
Yes	522	495			522	495		

Notes: Log-rank p -values were calculated by Chi-Square test. Bold type indicated statistical significance ($p < 0.05$).

Abbreviations: WHO, World Health Organization; NTR, Near-total resection; STR, Sub-total resection; GTR, Gross-total resection.

Table 2 The Basic Information About Selected SNPs

SNP-ID	Chr	Gene	Position	Alleles	MAF		p-value HWE	OR (95% CI)	p-value
					Case	Control			
rs9369269	6	<i>TREM1</i>	41236513	A/C	0.530	0.491	0.475	1.17(0.99–1.39)	0.070
rs4714447	6	<i>TREM1</i>	41239822	C/T	0.339	0.355	0.696	0.93(0.78–1.12)	0.442
rs2170887	6	<i>TREM1</i>	41241292	C/A	0.504	0.487	0.476	1.07(0.90–1.27)	0.447
rs2234242	6	<i>TREM1</i>	41244020	C/G/T	0.259	0.268	0.649	0.95(0.78–1.16)	0.623
rs1351835	6	<i>TREM1</i>	41244499	T/A	0.250	0.265	0.488	0.92(0.76–1.12)	0.414
rs2234237	6	<i>TREM1</i>	41250466	T/A	0.311	0.311	0.602	1.00(0.83–1.20)	0.984

Notes: p-value was calculated by Pearson's chi-square test. Bold type indicates statistical significance ($p < 0.05$).

Abbreviations: SNP, Single nucleotide polymorphism; Chr, Chromosome; MAF, Minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3 The Overall Association Analysis of *TREM1* Variants with Glioma Susceptibility in Genetic Models

SNP-ID	Model	Genotype	Frequency		With Adjustment	
			Case	Control	OR (95% CI)	p-value
rs9369269	Codominant	A/A	113	134	1	
		A/C	298	242	1.46(1.08–1.97)	0.014
		C/C	147	125	1.40(0.99–1.97)	0.058
	Dominant	A/A	113	134	1	
		C/C-A/C	445	367	1.44(1.08–1.91)	0.013
	Recessive	A/A-A/C	411	376	1	
		C/C	147	125	1.08(0.82–1.42)	0.590
	Log-additive	–	–	–	1.18(0.99–1.40)	0.065
rs4714447	Codominant	C/C	240	210	1	
		C/T	254	224	0.82(0.55–1.20)	0.944
		T/T	61	65	0.99(0.77–1.28)	0.331
	Dominant	C/C	240	210	1	
		T/T-C/T	315	289	0.95(0.75–1.22)	0.699
	Recessive	C/T-C/C	494	434	1	
		T/T	61	65	0.83(0.57–1.20)	0.314
	Log-additive	–	–	–	0.93(0.78–1.12)	0.441
rs2170887	Codominant	C/C	131	136	1	
		C/A	292	243	1.14(0.81–1.61)	0.142
		A/A	135	123	1.25(0.93–1.67)	0.450
	Dominant	C/C	131	136	1	
		A/A-C/A	427	366	1.21(0.92–1.60)	0.176
	Recessive	C/A-C/C	423	379	1	
		A/A	135	123	0.99(0.74–1.31)	0.919
	Log-additive	–	–	–	1.07(0.90–1.27)	0.439
rs2234242	Codominant	G/G	307	270	1	
		G/A	209	192	0.90(0.56–1.45)	0.748
		A/A	39	38	0.96(0.74–1.24)	0.671
	Dominant	G/G	307	270	1	
		A/A-G/A	248	230	0.95(0.74–1.21)	0.676
	Recessive	A/A-G/G	516	462	1	
		A/A	39	38	0.92(0.58–1.46)	0.716
	Log-additive	–	–	–	0.95(0.79–1.16)	0.630

(Continued)

Table 3 (Continued).

SNP-ID	Model	Genotype	Frequency		With Adjustment	
			Case	Control	OR (95% CI)	p-value
rs1351835	Codominant	T/T	308	270	1	
		T/A	208	186	0.76(0.46–1.25)	0.856
		A/A	33	38	0.98(0.75–1.26)	0.283
	Dominant	T/T	308	270	1	
		A/A-T/A	241	224	0.94(0.74–1.20)	0.621
	Recessive	T/A-T/T	516	456	1	
		A/A	33	38	0.77(0.47–1.25)	0.289
	Log-additive	–	–	–	0.92(0.76–1.12)	0.409
		–	–	–	–	–
rs2234237	Codominant	T/T	272	240	1	
		T/A	224	209	1.05(0.70–1.59)	0.665
		A/A	61	51	0.94(0.73–1.22)	0.803
	Dominant	T/T	272	240	1	
		A/A-T/A	285	260	0.97(0.76–1.23)	0.780
	Recessive	T/A-T/T	496	449	1	
		A/A	61	51	1.08(0.73–1.60)	0.697
	Log-additive	–	–	–	1.00(0.83–1.20)	0.977
		–	–	–	–	–

Notes: p-value was calculated by logistic regression analysis adjusted for gender and age. Bold type indicate statistical significance ($p < 0.05$).

Abbreviations: SNP, Single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

Besides, age- and gender-stratified analyses were completed to explore the influence of *TREMI* polymorphisms on glioma risk (Table 4). Compared with the C/T-C/C genotype, the T/T genotype of rs4714447 in *TREMI* could remarkably decrease the risk of glioma in patients aged >40 years in the recessive model (adjusted OR = 0.59, 95% CI: 0.35–0.99, $p = 0.046$), while rs9369269 was associated with a reduced risk of glioma (adjusted OR = 0.62, 95% CI: 0.40–0.95, $p = 0.028$) in patients aged ≤40 years. Furthermore, rs9369269 was found to be related to glioma risk in females (codominant model: adjusted OR = 1.94, 95% CI: 1.13–3.35, $p = 0.017$; dominant model: adjusted OR = 1.62, 95% CI: 1.05–2.50, $p = 0.029$; log-additive model: adjusted OR = 1.40, 95% CI: 1.06–1.83, $p = 0.016$), but no significance was observed in males.

Further, we assessed the association between *TREMI* polymorphisms and clinical features of patients [Supplementary Tables 2–4](#). As shown in [Supplementary Table 2](#), while comparing patients with astrogloma and healthy subjects, subjects with rs9369269 A/C genotype were more likely to suffer from glioma than people with A/A genotype in the codominant model (adjusted OR = 1.39, 95% CI: 1.01–1.91, $p = 0.045$). While comparing patients with WHO grades I–II and patients with WHO grades III–IV, we observed a significant association between rs1351835 and a reduced risk of glioma, as shown in [Supplementary Table 3](#) (adjusted OR = 0.38, 95% CI: 0.15–0.93, $p = 0.035$). In the [Supplementary Table 4](#), we performed the multivariate analysis of associations among SNP genotypes, various factors, OS and PFS. As for rs1351835, compared to T/T genotype carriers, carriers with A/T genotype were significantly associated with OS (HR = 0.81, 95% CI: 0.67–0.97, $p = 0.025$), but not with PFS (HR = 0.86, 95% CI: 0.71–1.04, $p = 0.119$). Significant associations between rs9369269, rs4714447, rs2170887, rs2234242 and rs2234237 and OS, PFS were not observed.

SNP-SNP Interaction Was Used to Predict the Glioma Risk

In the [Supplementary Table 5](#), MDR analysis showed that the model composed of rs9369269, rs4714447, rs2170887, rs2234242, rs1351835 and rs2234237, with 10/10 cross-validation consistency (CVC), the training accuracy of 61.39% and the testing accuracy of 49.3%, might be the best model to predict glioma risk ($p < 0.001$). The circle graph (Figure 2) indicates a positive interaction between rs2234242 and rs4714447, with the information gain (Ig) value of 0.2%. Rs430615 was also correlated with rs1351835 and rs2170887, with Ig value of 0.02%, 0.02%, respectively.

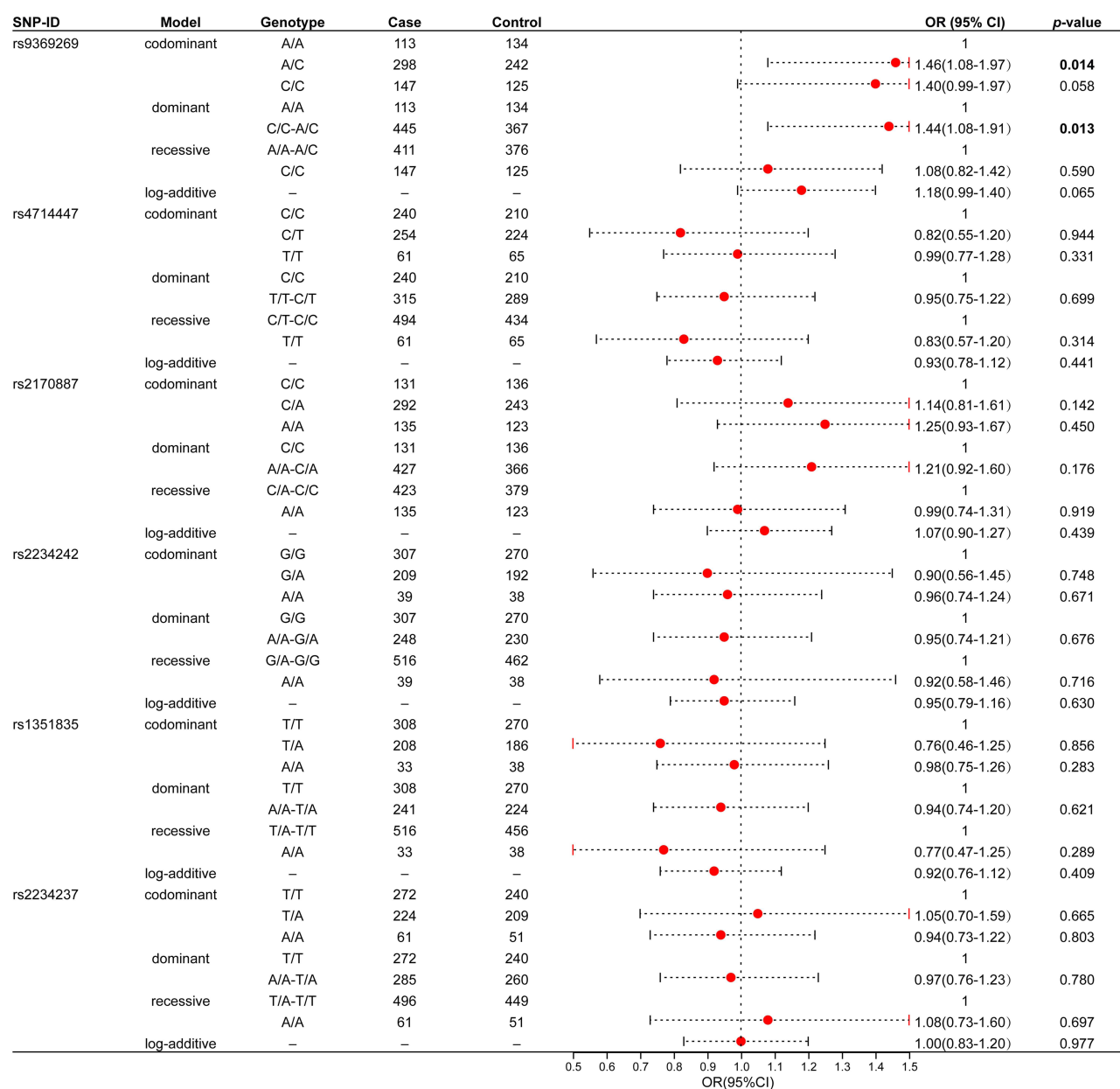


Figure I Overall analyses for the association between *TREM1* variants and glioma susceptibility.

Abbreviations: CI, Confidence interval; OR, Odds ratio.

Discussion

In this study, overall results illustrated that *TREM1* rs9369269 was related to an increased glioma risk. Rs9369269 was also related to the risk of glioma in patients aged ≤ 40 years and females. Subjects with rs9369269 AC genotype were more susceptible to suffer glioma compared with people with CC genotype (patients with astrogloma vs healthy people). As for rs1351835, compared to TT genotype carriers, carriers with AT genotype were significantly associated with OS. Therefore, polymorphisms of *TREM1* were important in the development and prognosis of glioma.

TREM1, also called *CD354*, is located in the chromosome of 6p21.1. *TREM1* has been reported to enlarge the inflammatory response and act as a key mediator of inflammation. According to the report, elevated serum/plasma levels of sTREM-1 have been found in infectious and non-infectious inflammatory diseases.^{9,18} *TREM1* downregulation can inhibit sepsis in mice.¹⁹ However, Mansur et al have²⁰ reported that there was no association between the SNP-rs2234237- and the clinical course of sepsis in critically ill Caucasus patients. No correlation between rs2234237 and

Table 4 The Association Between rs9369269 and rs4714447 and Glioma Susceptibility After Age- and Gender-Stratified Analyses

SNP	Model	Genotype	≥40		≤40		Male		Female	
			OR (95% CI)	p-value	OR (95% CI)	p-value	OR(95% CI)	p-value	OR(95% CI)	p-value
rs9369269	Codominant	A/A	1		1		1		1	
		A/C	1.41(0.92–2.15)	0.113	1.31(0.86–2.01)	0.213	1.28(0.87–1.89)	0.203	1.50(0.96–2.37)	0.077
		C/C	1.59(0.98–2.57)	0.060	0.74(0.44–1.24)	0.254	0.89(0.56–1.4)	0.605	1.94(1.13–3.35)	0.017
	Dominant	A/A	1		1		1		1	
		C/C-A/C	1.47(0.99–2.18)	0.058	1.11(0.74–1.66)	0.611	1.14(0.79–1.63)	0.485	1.62(1.05–2.50)	0.029
	Recessive	A/A-A/C	1		1		1		1	
		C/C	1.27(0.86–1.88)	0.236	0.62(0.40–0.95)	0.028	0.76(0.52–1.11)	0.158	1.46(0.94–2.27)	0.093
rs4714447	Log-additive	–	1.26(0.99–1.60)	0.061	0.88(0.68–1.13)	0.316	0.96(0.76–1.20)	0.692	1.40(1.06–1.83)	0.016
	Codominant	C/C	1		1		1		1	
		T/C	1.02(0.70–1.47)	0.932	0.98(0.68–1.43)	0.926	0.99(0.70–1.41)	0.965	0.99(0.68–1.45)	0.955
		T/T	0.60(0.34–1.03)	0.064	1.07(0.59–1.94)	0.827	0.79(0.48–1.31)	0.359	0.87(0.46–1.66)	0.673
	Dominant	C/C	1		1		1		1	
		T/T-C/T	0.90(0.64–1.27)	0.551	1.00(0.70–1.42)	0.992	0.94(0.68–1.31)	0.712	0.97(0.67–1.39)	0.860
	Recessive	C/T-C/C	1		1		1		1	
		T/T	0.59(0.35–0.99)	0.046	1.08(0.61–1.90)	0.792	0.79(0.49–1.27)	0.335	0.88(0.48–1.61)	0.671
	Log-additive	–	0.83(0.65–1.07)	0.158	1.15(0.88–1.50)	0.906	0.91(0.72–1.16)	0.457	0.95(0.72–1.26)	0.741

Notes: p-value was calculated by logistic regression analysis adjusted for gender and age. Bold type indicated statistical significance ($p < 0.05$).

Abbreviations: SNP, Single nucleotide polymorphism; OR, odds ratio; 95% CI, 0.95% confidence interval.

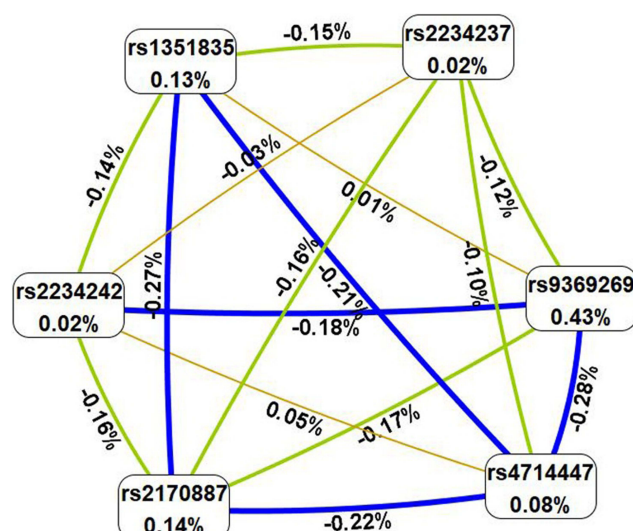


Figure 2 Multifactor dimensionality reduction (MDR) was completed to assess the interaction among SNPs in *TREM1* to predict glioma risk.

sepsis patients' survival was detected. However, Su et al have discovered that the *TREM1* expression level in the non-survival group was significantly higher than that in the survival group. *TREM1* rs2234237 was also related to the prognosis of Chinese patients with sepsis, so it may be a risk factor for sepsis prognosis in Chinese individuals.²¹ The above results have shown that the association of *TREM1* rs2234237 with sepsis is associated with the study population. In our study, *TREM1* rs2234237 was first discovered to be related to the risk of glioma. However, we did not find a significant correlation between this locus and OS and PFS through multivariate analysis, and no significant correlation was found between rs2234237 and OS and PFS. In the future, we still need to explore the correlation between the *TREM1* polymorphisms and OS and PFS through larger samples and extensive experiments.

The present study has some shortcomings. The collection of samples mainly concentrated in the Han nationality, and people of different races are needed to be collected for verification of the results. And the source of sample was mainly in one hospital, so glioma patients and healthy people from multiple hospitals are needed to be collected to verify the results. Besides, on the basis of the GEPIA database (<http://gepia.cancer-pku.cn/>), the association between *TREM1* expression level and the prognosis of lower grade glioma was observed ([Supplementary Figure 1](#)). We need to continue to collect samples to verify the results, laying a theoretical foundation for the mechanism of *TREM1* and its sites in the pathogenesis of glioma.

Data Sharing Statement

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Our research was approved by the ethics committee of the Xi'an Chang'an District Hospital and Northwest University, and all participants signed informed consent.

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Disclosure

The authors have declared that they have no conflicts of interest in this work.

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