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Correlations of IL-18 and IL-6 gene polymorphisms and expression levels with onset of glioma

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Abstract. – OBJECTIVE: The aim of this study was to explore the correlations of interleukin (IL)-18 and IL-6 gene polymorphisms and expression levels with the onset of glioma.

PATIENTS AND METHODS: The differences in the expression levels of IL-18 and IL-6 between glioma patients and normal people in the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases were analyzed. A total of 200 glioma patients and 200 healthy people were taken as the research subjects. Peripheral blood was collected to extract deoxyribonucleic acids (DNAs). IL-18 and IL-6 gene polymorphisms were detected and analyzed combined with haplotype analysis and gene expression levels of IL-18 and IL-6, as well as their levels in serum.

RESULTS: Both IL-18 and IL-6 were highly expressed in tumor tissues of glioma patients, whereas they were lowly expressed in normal cerebral tissues, with statistically significant differences (p<0.05). Statistically significant differences in the allele distributions of IL-18 gene polymorphisms rs371411440 (p=0.041) and rs371828055 (p=0.002) and IL-6 gene polymorphisms rs201211345 (p=0.000) and rs201439472 (p=0.003) were observed between disease group and control group (p<0.05). Genotype distributions of IL-18 gene polymorphism rs371828055 (p=0.005) and IL-6 gene polymorphisms rs201211345 (p=0.000) and rs201439472 (p=0.019) in disease group were significantly different from those in control group (p<0.05). Disease group exhibited significantly higher frequencies of genotype GG of IL-18 gene polymorphism rs371828055, genotype AA of IL-6 gene polymorphism rs201211345 and genotype TT of IL-6 gene polymorphism rs201439472 than control group (p<0.05). There were statistically significant differences in the distributions of the dominant model AA+AC of IL-6 gene polymorphism rs201211345 (p=0.016) and the recessive model GT+TT of IL-18 gene polymorphism rs371828055 (p=0.010) between the two groups (p<0.05). Differences in the distributions of haplotypes CC (p=0.001) and GT (p=0.027) of IL-18 gene polymorphisms rs371411440 and rs371828055 and haplotypes AC (p=0.009), AT (p=0.000) and CT (p=0.000) of IL-6 gene polymorphisms rs201211345 and rs201439472 were observed between disease group and control group (p<0.05). In addition, a high degree of linkage disequilibrium was detected between IL-6 gene polymorphisms rs201211345 and rs201439472 (D'=0.583). The genotypes of IL-18 gene polymorphism rs371828055 were evidently correlated with the gene expression of IL-18 (p=0.000). Meanwhile, patients with genotype GT had a distinctly lower expression level of IL-18 (p<0.05). The genotypes of IL-6 gene polymorphism rs201211345 were obviously associated with the expression of IL-6 (p=0.002). The expression of IL-6 was markedly down-regulated in patients carrying genotype AA (p<0.05). Consistent with the expression levels of IL-18 and IL-6, the genotypes of IL-18 gene polymorphism rs371828055 were associated with the content of serum IL-18 (p<0.05). Moreover, patients carrying genotype GT had distinctly lower content of serum IL-18 (p<0.05). Additionally, the genotypes of IL-6 gene polymorphism rs201211345 were evidently correlated with the content of serum IL-6 (p<0.05), and the content of serum IL-6 declined distinctly in patients with genotype AA (p<0.05).

CONCLUSIONS: IL-18 and IL-6 gene polymorphisms and expression levels are significantly correlated with the onset of glioma.

Key Words:
IL-18, IL-6, Gene polymorphism, Glioma.

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Introduction

Glioma is a tumor originating from the brain, with an annually increasing morbidity rate[1,2]. As one of the leading causes of death in young and mid-aged people, glioma remains the most common malignancy that accounts for about half of intracranial tumor cases[3,4]. This disease is mainly classified into astrocytoma, glioblastoma and ependymoma. Among all types, glioblastoma is the most sever one, with obvious symptoms of high intracranial pressure and the seizure of epilepsy and other mental diseases[5]. Currently, the pathogenesis of glioma remains elusive. Therefore, it is of great significance to explore its pathogenesis and susceptibility.

Gene polymorphism, a crucial genetic form in biology[6], affects the development and progression of multiple diseases, such as paranoid schizophrenia[7] and chronic kidney disease[8]. It has been corroborated that cytokines, critical components in the immune system, can influence the development of glioma[9]. Among them, both IL-18 and IL-6 have a pivotal regulatory effect on immunity. Meanwhile, their gene polymorphisms may affect the onset of glioma. Therefore, in the present study, we explored the correlations of IL-18 and IL-6 gene polymorphisms and expression levels with the onset of glioma.

Patients and Methods

General Data

A total of 200 glioma patients who received treatment in our hospital in recent years were enrolled in disease group (n=200). Meanwhile, 200 healthy people receiving physical examinations in our hospital were enrolled in control group (n=200). The selection of patients was based on the guideline proposed by the Union for International Cancer Control (UICC). General and clinical data were collected from subjects in both groups, including name, ID No., age, sex, BMI, medical history, family history of tumors and history of drug allergies. Control group consisted of 121 males and 79 females, with the mean age of (45.16±2.56) years old. Meanwhile, there were 122 males and 88 females in disease group, with the mean age of (43.25±2.19) years old. No statistically significant differences were observed in the general data, such as age and sex distribution, between the two groups ($p<0.05$). Patients in disease group were diagnosed by doctors with higher-than-intermediate professional titles based on CT and MRI results. This study was approved by the Ethics Committee of Chinese PLA (People's Liberation Army) General Hospital. Signed written informed consents were obtained from the patients and/or guardians.

Collection and Processing of Samples

About 5 mL of peripheral blood was first drawn from disease group and control group. Within 1 h, collected blood samples were centrifuged at 3,000 rpm for 5 min. The upper-layer serum and mid-layer nucleated cells were separately transferred into new centrifuge tubes. Subsequently, the upper-layer serum was stored in liquid nitrogen for determining IL levels. Meanwhile, mid-layer nucleated cells were subjected to the extraction of genomic deoxyribonucleic acids (DNAs).

Genomic DNA Extraction and Polymerase Chain Reaction (PCR) Amplification

Genomic DNAs were first extracted from the peripheral blood in both disease group and control group using the blood genome extraction kit (TIANGEN, Beijing, China). The regions of IL-18 gene polymorphisms rs371411440 and rs371828055, and IL-6 gene polymorphisms rs201211345 and rs201439472 were amplified using a PCR instrument strictly according to the instructions of the kit. Specifically, the PCR was performed in a 25 μL system composed of 1 μL of forward primers (50 μmol), 1 μL of reverse primers (50 μmol), 0.5 μL of DNA templates (100 ng), 12.5 μL of Taq polymerase and 10 μL of dH_2O. Procedures for reaction were as follows: 95°C for 5 min, (95°C for 30 s, 54°C for 45 s and 72°C for 30 s) ×40 cycles, 72°C for 5 min, and heat preservation at 4°C. Primers of gene polymorphisms were listed in Table I. Finally, the amplified PCR products were analyzed by electrophoresis with a SYBR Safe (Molecular Probes, Eugene, OR, USA) 2% agarose gel and visualized in a UV transilluminator.

Determination of Serum IL-18 and IL-6 Levels

The levels of serum IL-18 and IL-6 were determined using enzyme-linked immunosorbent assay (ELISA). Serum samples were first taken out from the liquid nitrogen and thawed slowly in a refrigerator at 4°C. The levels of serum IL-18 and IL-6 in disease group and control group were then measured according to the instructions of ELISA kit (Invitrogen Corporation, Carlsbad, CA, USA) and Luminex 300 system (Luminex Corporation,

Table I. PCR primer sequences.

	Forward/reverse	Primer sequence
rs371411440	Forward	TTTTGCCAAGGAGTGCTAAAGA
	Reverse	AACCCTCTGCACCCAGTTTTC
rs371828055	Forward	ACTGAGAGTGATTGAGAGTGGAC
	Reverse	AACCCTCTGCACCCAGTTTTC
rs201211345	Forward	TGAGCAGGATGGAGAATTACAGG
	Reverse	GTCCAAGTTCATCTTCTAGGCAC
rs201439472	Forward	TCTGCGGCATGTTCTGGATTT
	Reverse	ATGTGTTGTCAGAGCCCTTTAG
IL-18	Forward	GTGCTCCTTGTCAACAGCG
	Reverse	GGGGAGTTTCAGGTTCCTGTA
IL-6	Forward	TACAAGAACCCGAAACTGACTCG
	Reverse	ACATGAAGGTAGTCTCACTGCC
GAPDH	Forward	TCCTGTCTTGCATTGCACTAAG
	Reverse	CATCCTGGTGAGTTTGGGATTC

San Diego, CA, USA). In this assay, the mean sensitivity was <0.49 pg/mL, and the inter-batch coefficient of variation was 5.7%.

Measurement of IL-18 and IL-6 Expression Levels

The expression levels of IL-18 and IL-6 were measured using real-time quantitative polymerase chain reaction (RT-qPCR). Briefly, total RNA was extracted from peripheral blood nucleated cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted RNA was reversely transcribed into complementary deoxyribose nucleic acids (cDNAs). The expression levels of IL-18 and IL-6 were determined *via* RT-qPCR. Primer sequences of IL-18, IL-6 and the internal reference glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were shown in Table I.

Bioinformatics Analysis

The expression levels of IL-18 and IL-6 in glioma patients and normal people in the TCGA and GTEx databases were analyzed using the GEPIA2 website tool, and the differences were analyzed and visualized.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 24.0 (IBM, Armonk, NY, USA) was employed for statistical analysis. Measurement data were compared using *t*-test, and intergroup comparisons were made using analysis of variance. Besides, Hardy-Weinberg equilibrium test was performed. Haplotypes were analyzed at the SHEsis website. $p<0.05$ was considered statistically significant.

Results

Differences in the Expression Levels of IL-18 and IL-6 Between Glioma Patients and Normal People

Both IL-18 and IL-6 were highly expressed in tumor tissues of glioma patients, whereas they were lowly expressed in normal cerebral tissues, with statistically significant differences ($p<0.05$) (Figure 1A and 1B).

Allele Distributions of IL-18 Gene Polymorphisms rs371411440 and rs371828055 and IL-6 Gene Polymorphisms rs201211345 and rs201439472

Statistically significant differences were observed in allele distributions of IL-18 gene polymorphisms rs371411440 ($p=0.041$) and rs371828055 ($p=0.002$) and IL-6 gene polymorphisms rs201211345 ($p=0.000$) and rs201439472 ($p=0.003$) between disease group and control group (Table II).

Genotype Distributions of IL-18 Gene Polymorphisms rs371411440 and rs371828055 and IL-6 Gene Polymorphisms rs201211345 and rs201439472

Genotype distributions of IL-18 gene polymorphisms rs371828055 ($p=0.005$) and IL-6 gene polymorphisms rs201211345 ($p=0.000$) and rs201439472 ($p=0.019$) in disease group were significantly different from those in control group (Table III). Disease group exhibited significantly higher frequencies of genotype GG of IL-18 gene

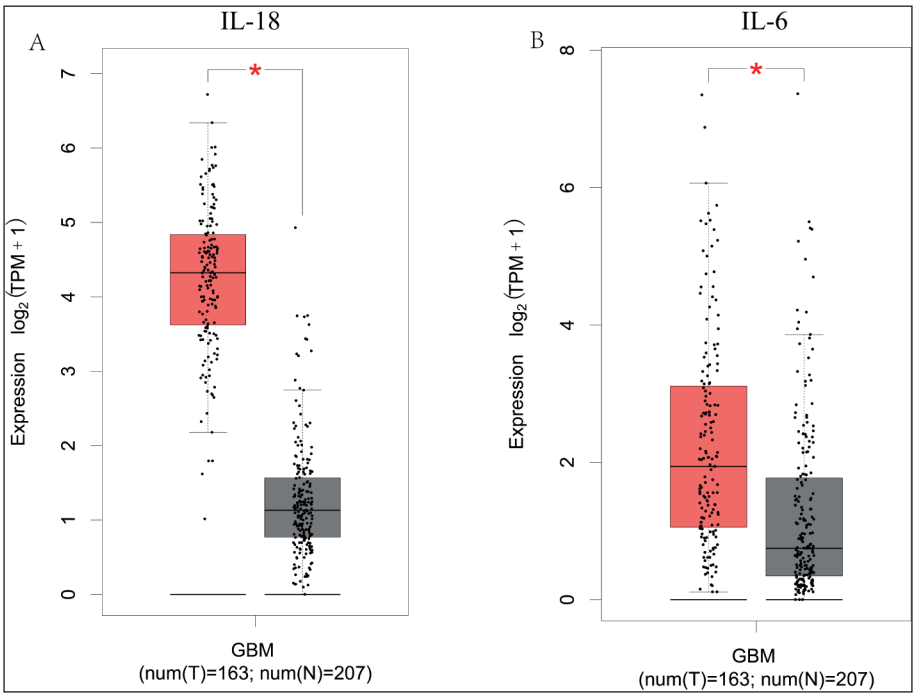

Figure 1. Differences in the expression levels of IL-18 (**A**) and IL-6 (**B**) between glioma patients and normal people. GBM: glioblastoma multiforme, T: tumor tissues (TCGA database), and N: normal tissues (GTEx database) (*p<0.05).

polymorphism rs371828055, genotype AA of IL-6 gene polymorphism rs201211345 and genotype TT of IL-6 gene polymorphism rs201439472 than control group (p<0.05).

Analysis of IL-18 Gene Polymorphisms rs371411440 and rs371828055 and IL-6 Gene Polymorphisms rs201211345 and rs201439472

According to the gene polymorphism analysis results, the distributions of the dominant model AA+AC of IL-6 gene polymorphism rs201211345 (p=0.016) and the recessive model GT+TT of IL-18 gene polymorphism rs371828055 (p=0.010) in disease group were significantly different from those in control group (Table IV).

Analysis of Haplotypes of IL-18 Gene Polymorphisms rs371411440 and rs371828055 and IL-6 Gene Polymorphisms rs201211345 and rs201439472

Haplotype analysis indicated that statistically significant differences were observed in the distributions of haplotypes CC (p=0.001) and GT (p=0.027) of IL-18 gene polymorphisms rs371411440 and rs371828055 and haplotypes AC (p=0.009), AT (p=0.000) and CT (p=0.000) of IL-6 gene polymorphisms rs201211345 and rs201439472 between disease group and control group (Table V). Besides, linkage disequilibrium analysis results revealed that there was a high degree of linkage disequilibrium between IL-6 gene polymorphisms rs201211345 and rs201439472 (D'=0.583) (Table VI).

Correlations of IL-18 and IL-6 Gene Polymorphisms with their Gene Expression Levels

Genotypes of IL-18 gene polymorphism rs371828055 were evidently correlated with the expression of IL-18 (p=0.000). Patients with genotype GT had a distinctly lower expression level of IL-18 (p<0.05). Likewise, genotypes of IL-6 gene polymorphism rs201211345 were markedly associated with the gene expression of IL-6 (p=0.002), and the expression of IL-6 was significantly lowered in patients carrying genotype AA (p<0.05, Table VII).

Correlations of IL-18 Gene Polymorphism rs371828055 and IL-6 Gene Polymorphism rs201211345 with the Levels of Serum IL-18 and IL-6

Consistent with the expression levels of IL-18 and IL-6, genotypes of IL-18 gene polymorphism

Table II. Allele distributions of IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472.

Gene	Polymorphism	Allele	Control group	Disease group	Odd ratio (OR)	95% confidential interval (CI)	χ^2	*p*
IL-18	rs371411440	C	184 (0.460)	213 (0.532)	1.33	1.01-1.76	4.21	0.041
		G	216 (0.540)	187 (0.468)				
	rs371828055	G	191 (0.477)	234 (0.585)	1.54	1.16-2.03	9.28	0.002
		T	209 (0.522)	166 (0.415)				
IL-6	rs201211345	A	200 (0.500)	261 (0.652)	1.87	1.41-2.49	19.04	0.000
		C	200 (0.500)	139 (0.347)				
	rs201439472	C	199 (0.497)	158 (0.395)	0.65	0.49-0.87	8.52	0.003
		T	201 (0.502)	242 (0.605)				

rs371828055 were associated with the content of serum IL-18 ($p<0.05$). Patients carrying genotype GT had distinctly lower content of serum IL-18 ($p<0.05$, Figure 2). Additionally, genotypes of IL-6 gene polymorphism rs201211345 were evidently correlated with the content of serum IL-6 ($p<0.05$), and patients with genotype AA had evidently lower content of serum IL-6 ($p<0.05$, Figure 3).

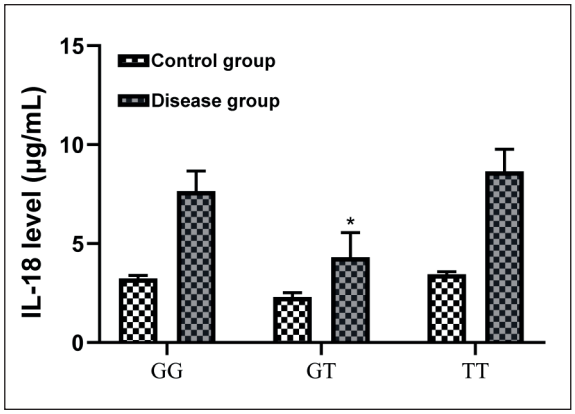

Figure 2. Correlation between IL-18 gene polymorphism rs371828055 and serum IL-18 level (*$p<0.05$).

Discussion

Glioma is one of the major life-threatening brain tumors, which greatly hinders the growth of social economy[10,11]. According to the mortality rate rankings published by the World Health Organization, malignant glioma is the second leading cause of death in tumor patients under the age of 34 years old. Glioma is mainly characterized by related symptoms of higher intracranial pressure, including dizziness, headache, projectile vomiting, epileptic seizure, and even disturbance of consciousness and hemiplegia[9]. Some diseases including neurofibromatosis and tuberous sclerosis may be the susceptibility factor for glioma[12]. Current studies have found that environmental factors, such as the use of mobile phone and ionizing radiation, are probably contributors to this

Table III. Genotype distributions of IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472.

Gene	Polymorphism	Genotype	Control group	Disease group	χ^2	*p*
IL-18	rs371411440	CC	39 (0.195)	59 (0.295)	5.48	0.064
		CG	106 (0.530)	95 (0.475)		
		GG	55 (0.275)	46 (0.230)		
	rs371828055	GG	47 (0.235)	77 (0.385)	10.59	0.005
		GT	97 (0.485)	80 (0.400)		
		TT	56 (0.280)	43 (0.215)		
IL-6	rs201211345	AA	55 (0.275)	89 (0.445)	17.09	0.000
		AC	90 (0.450)	83 (0.415)		
		CC	55 (0.275)	28 (0.140)		
	rs201439472	CC	56 (0.280)	35 (0.175)	7.83	0.019
		CT	87 (0.435)	88 (0.440)		
		TT	57 (0.285)	77 (0.385)		

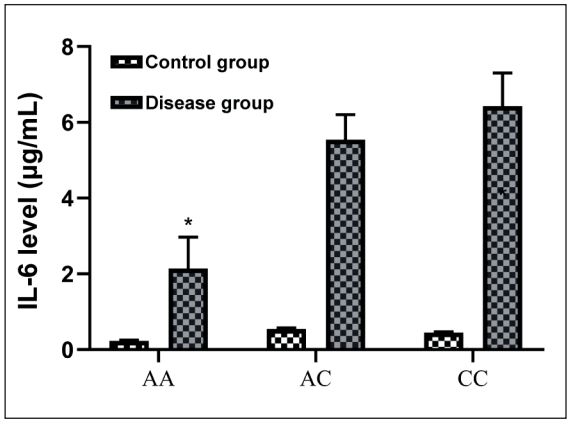

Figure 3. Correlation between IL-6 gene polymorphism rs201211345 and serum IL-6 level (*p<0.05).

disease. Additionally, the most common drivers for the development of tumors, the changes in genetic characters are one of the important causes of glioma[13]. Gene polymorphisms have been proven to be largely correlated with the development of glioma, including ANXA5[14] and RTEL1[15]. Therefore, exploration of the correlation between gene polymorphism and the onset of glioma has important implications for elucidating its pathogenesis.

ILs are considered as important components with vital regulatory effects on the proliferation, differentiation and function of immunocytes[16]. Among them, IL-18 can stimulate the secretion of numerous cytokines by multiple immunocytes and facilitate the proliferation of Th1 cells. Moreover, it can work with IL-12 to induce the production of IFN-γ in cells, exerting a synergy[17]. IL-6, a pleiotropic IL, can be produced by various non-immune cells and immune cells to regulate vascular responses substance metabolisms mitochondrial activities and acute-phase responses[18]. Multiple studies have demonstrated that IL-18 and IL-6 gene polymorphisms affect the development and progression of various diseases[19,20]. In the present study, IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472 in peripheral blood nucleated cells were detected in 200 glioma patients and 200 healthy people. It was found that the allele distributions of IL-18 gene polymorphisms rs371411440 (p=0.041) and rs371828055 (p=0.002) and IL-6 gene polymorphisms rs201211345 (p=0.000) and rs201439472 (p=0.003) in disease group were significantly different from those in control group. Statistically significant differences were also observed in the genotype distributions of IL-18 gene polymorphisms rs371828055 (p=0.005) and rs201211345 (p=0.000) and rs201439472 (p=0.019) between disease group and control group. Meanwhile, disease group exhibited significantly higher frequencies of genotype GG of IL-18 gene polymorphism rs371828055, genotype AA of IL-6 gene polymorphism rs201211345 and genotype TT of IL-6 gene polymorphism rs201439472 than control group. The above results imply that IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472 are truly able to affect the onset of glioma, serving as important susceptibility factors.

Table IV. Analysis of IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472.

	Gene	Polymorphism	Genotype	Control group	Disease group	χ^2	p
Dominant model	IL-18	rs371411440	CC+CG	145 (0.725)	154 (0.770)	4.29	0.117
			GG	55 (0.275)	46 (0.230)		
		rs371828055	GG+GT	144 (0.720)	157 (0.785)	3.7	0.157
			TT	56 (0.280)	43 (0.215)		
	IL-6	rs201211345	AA+AC	145 (0.725)	172 (0.860)	8.24	0.016
			CC	55 (0.275)	28 (0.140)		
		rs201439472	CC+CT	143 (0.715)	123 (0.615)	5.87	0.053
			TT	57 (0.285)	77 (0.385)		
Recessive model	IL-18	rs371411440	CC	39 (0.195)	59 (0.295)	4.73	0.094
			CG+GG	161 (0.805)	141 (0.705)		
		rs371828055	GG	47 (0.235)	77 (0.385)	5.32	0.010
			GT+TT	153 (0.765)	123 (0.615)		
	IL-6	rs201211345	AA	55 (0.275)	89 (0.445)	9.24	0.070
			AC+CC	145 (0.725)	111 (0.555)		
		rs201439472	CC	56 (0.280)	35 (0.175)	3.77	0.152
			CT+TT	144 (0.720)	165 (0.825)		

Table V. Analysis of haplotypes of IL-18 gene polymorphisms rs371411440 and rs371828055 and IL-6 gene polymorphisms rs201211345 and rs201439472.

Gene	PHaplotype	Control group	Disease group	OR	CI	χ^2	*p*
IL-18	CC	95.82 (0.240)	140.21 (0.351)	1.713	1.259-2.331	11.841	0.001
	CT	88.18 (0.220)	72.79 (0.182)	0.787	0.556-1.113	1.841	0.175
	GG	95.18 (0.238)	93.79 (0.234)	0.981	0.708-1.359	0.013	0.908
	GT	120.82 (0.302)	93.21 (0.233)	0.702	0.512-0.962	4.863	0.027
IL-6	AC	117.77 (0.294)	85.78 (0.214)	0.654	0.474-0.902	6.744	0.009
	AT	82.23 (0.206)	175.22 (0.438)	3.012	2.203-4.119	49.528	0.000
	CC	81.23 (0.203)	72.22 (0.181)	0.865	0.608-1.230	0.654	0.419
	CT	118.77 (0.297)	66.78 (0.167)	0.475	0.338-0.666	18.968	0.000

Table VI. Linkage disequilibrium analysis.

D′	rs371411440	rs371828055	rs201211345	rs201439472
rs371411440	-	0.087	0.001	0.003
rs371828055	0.087	-	0.002	0.001
rs201211345	0.001	0.002	-	0.583
rs201439472	0.003	0.001	0.583	-

Table VII. Correlations of IL-18 and IL-6 gene polymorphisms with their gene expression levels.

Gene	Polymorphism	Genotype	Relative expression level of IL-18	*p*	Relative expression level of IL-6	*p*
IL-18	rs371411440	CC	16.42±2.45	0.214	65.18±5.35	0.231
		CG	16.45±1.31		64.32±3.54	
		GG	17.25±2.42		65.86±3.17	
	rs371828055	GG	19.84±1.24	0.000	65.33±2.14	0.437
		GT	12.31±0.98		64.35±3.82	
		TT	20.17±1.01		66.32±4.12	
IL-6	rs201211345	AA	16.32±1.24	0.421	56.31±4.12	0.002
		AC	16.57±2.12		72.98±3.12	
		CC	16.87±2.14		75.21±4.96	
	rs201439472	CC	16.72±1.26	0.591	63.12±3.15	0.121
		CT	16.12±1.52		64.81±4.48	
		TT	16.84±1.22		66.38±5.12	

According to the findings in the analyses of haplotypes and polymorphisms, the distributions of the dominant model AA+AC of IL-6 gene polymorphism rs201211345 (p=0.016) and recessive model GT+TT of IL-18 gene polymorphism rs371828055 (p=0.010) in disease group were significantly different from those in control group. Besides, statistically significant differences were observed in the distributions of haplotypes CC (p=0.001) and GT (p=0.027) of IL-18 gene polymorphisms rs371411440 and rs371828055 and haplotypes AC (p=0.009), AT (p=0.000) and CT (p=0.000) of IL-6 gene polymorphisms rs201211345 and rs201439472 between disease group and control group. High degree of linkage disequilibrium was detected between IL-6 gene polymorphisms rs201211345 and rs201439472 (D'=0.583). It can be inferred from these results that the onset of glioma may be affected not only by a single gene polymorphism.

Furthermore, bioinformatics analysis discovered that both IL-18 and IL-6 were highly expressed in tumor tissues of glioma patients, whereas were lowly expressed in normal cerebral tissues, with statistically significant differences (p<0.05). This suggests that IL-18 and IL-6 may play an important role in the progression of glioma. Additionally, the correlations of gene polymorphism with the expression levels of IL-18 and IL-6 and their levels in serum were

analyzed. The results indicated that genotypes of IL-18 gene polymorphism rs371828055 were evidently correlated with the gene expression of IL-18 (p=0.000), and patients with genotype GT had a distinctly lower expression level of IL-18. Moreover, genotypes of IL-6 gene polymorphism rs201211345 were obviously associated with the gene expression of IL-6 (p=0.002), and the expression of IL-6 was obviously lowered in patients carrying genotype AA. Consistent with the expression levels of IL-18 and IL-6, the genotypes of IL-18 gene polymorphism rs371828055 were associated with the content of serum IL-18 (p<0.05), and the content of serum IL-18 declined distinctly in patients carrying genotype GT. Besides, the genotypes of IL-6 gene polymorphism rs201211345 were evidently correlated with the content of serum IL-6 (p<0.05), and patients with genotype AA had evidently lower content of serum IL-6.

Conclusions

The novelty of this study was that IL-18 and IL-6 gene polymorphisms and expression levels are obviously correlated with the onset of glioma.

Conflicts of Interest

The authors declare no conflicts of interest.

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