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The Impact of *PPARD* and *PPARG* Polymorphisms on Glioma Risk and Prognosis

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Recent studies showed that peroxisome proliferator-activated receptors (PPARs) had effects on the progression of multiple tumors, but the role of *PPARD* and *PPARG* in glioma remains poorly understand. We conducted a case-control study to investigate the association of polymorphisms in *PPARD* and *PPARG* with glioma risk and prognosis in the Chinese Han population. Seven polymorphisms (*PPARD*: rs2016520, rs67056409, rs1053049 and rs2206030; *PPARG*: rs2920503, rs4073770 and rs1151988) were genotyped using the Agena MassARRAY system in 568 glioma patients and 509 healthy controls. The odd ratios (OR) and 95% confidence interval (CI) were calculated to assess the association of *PPARD* and *PPARG* polymorphisms with glioma risk. The Multifactor dimensionality reduction (MDR) method was used to analysis interactions of genetic polymorphisms on glioma risk. Then, we conducted log-rank test, Kaplan-Meier analysis and Cox regression model to evaluate the relationship of *PPARD* and *PPARG* polymorphisms with glioma prognosis. We found *PPARD* polymorphisms (rs2016520, rs67056409, rs1053049) were significantly associated with glioma risk in multiple models ($P < 0.05$). Stratified analysis showed rs2016520, rs67056409, rs1053049 of *PPARD* significantly decreased risk of glioma in the subgroup of age > 40 and astrocytoma ($P < 0.05$). For male, *PPARD* rs1053049 had a strong relationship with glioma risk in allele ($P = 0.041$), dominant ($P = 0.040$) and additive ($P = 0.040$) models. The effect of *PPARG* rs2920503 on glioma risk was related to glioma grade ($P < 0.05$). MDR showed that a seven-locus model was the best polymorphisms interaction pattern. Moreover, surgery and chemotherapy had strongly impact on overall survival and progression free survival of glioma patients. Our findings suggested that *PPARD* and *PPARG* polymorphisms were associated with glioma risk and prognosis in the Chinese Han population, and further studies are need to confirm our results.

Glioma is the most common type of malignant brain tumors in the central nervous system (CNS), accounting for approximately 80% of primary brain tumors[1]. The incidence of brain cancer is the highest in European (5.5/100,000 persons), North America (5.3/100,000 persons), Australia (5.3/100,000 persons), Western Asia (5.2/100,000 persons) and Northern Africa (5.0/100,000 persons)[2]. In China, there were 1,016,000 newly diagnosed cases of brain and CNS tumor in 2015[3]. Glioma occurs varied in age, sex, race, histologic type and geographic characteristics[4]. And, glioma has poor overall survival (OS), with less than 5 year survival of patients after diagnosis[5]. The etiology of glioma is multifactorial, which is the results of environmental exposure and genetic factors[4]. Single nucleotide polymorphism (SNP) is the most studied mutations involved in genetic predisposition of glioma. Recently, increasing studies are focused on the role of Peroxisome proliferator-activated receptors (PPARs) polymorphisms on cancer.

PPARs is a subfamily of nuclear receptor transcription factors and consists three isoforms (PPARα, PPARδ and PPARγ). *PPARD* encodes PPARδ, a nuclear hormone receptor that implicated in varieties of biological processes, including epidermal cell proliferation, migration, lipid and glucose metabolism[6–8]. *PPARD* is highly expressed in brain, heart, skeletal muscle, adipose tissue and pancreatic islets[9]. In mice, *PPARD* agonists increase leptin secretion and improve type 2 diabetes[10,11]. The overexpression of *PPARD* was observed in various human cancers, such as colorectal, pancreatic and lung cancer[12–15]. Previous studies revealed that *PPARD* polymorphisms were associated with lipid levels, metabolic traits, obesity and risk of coronary heart diseases (CHD) and cancers[16–19]. *PPARD* rs2016520 is located in the 5′-untranslated region of exon, which has been widely studied in

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multiple physiological and pathological process[20–23]. However, little is known on the relationship of *PPARD* polymorphisms with glioma risk and prognosis.

PPARG is located in human chromosome 3p25 and encodes a nuclear receptor (PPARγ) activated by fatty acid metabolites or synthetic medicines[24–26]. *PPARG* is mainly expressed in suprabasal keratinocytes, adipocyte tissue, vascular endothelial cells, macrophage cells and smooth muscle cells[27,28]. *PPARG* regulates adipocyte differentiation and controls genes expression involved in lipid and glucose homeostasis[29]. And, *PPARG* has anti-inflammatory effect by restraining the production of inflammatory mediators[30]. It has been reported that *PPARG* is implicated in the pathology of obesity, diabetes, atherosclerosis and cancer. Wang *et al*. indicated that PPARG could arrest cell growth in human oral cancer[31]. Fan *et al*. pointed that anti- *PPARG* therapy is a potential strategy to improve endocrine-resistant breast cancer[32]. Nevertheless, the role of *PPARG* in glioma has not been elucidated.

Therefore, we conducted a case-control study to investigate the association of *PPARD* and *PPARG* polymorphisms (rs2016520, rs67056409, rs1053049, rs2206030, rs2920503, rs4073770 and rs1151988) with glioma risk and prognosis in the Chinese Han population.

Methods

Study population. This study consisted of 568 glioma patients and 509 healthy controls, recruited from the Second Affiliated Hospital of Xi'an Jiaotong University, Shaanxi Province, China. All glioma patients were newly diagnosed and histologically confirmed according to the World Health Organization (WHO) classification[33]. The exclusion criteria of glioma patients are as follows: (1) patients have history of cancer or CNS diseases; (2) patients are under 18 years old. The controls were healthy individuals without history of cancer or serious diseases who randomly enrolled from the same hospital. We obtained demographic and clinical information of study population from medical records and follow-up. This study was performed in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University. Informed consents were required form all participants before this study.

SNP selection and genotyping. Combined previously studies, we selected four SNPs of *PPARD* (rs2016520, rs67056409, rs1053049 and rs2206030) and three SNPs of *PPARG* (rs2920503, rs4073770 and rs1151988), with minor allele frequencies (MAF) greater than 5% in the HapMap Chinese Han Beijing population. We extracted DNA from peripheral blood samples using the blood DNA kit (GoldMag Co. Ltd., Xi′an, China). SNP genotyping was performed in the Agena MassARRAY system (Agena, San Diego, CA, USA). Primers for polymerase chain reaction (PCR) amplification and extension were designed by the Agena MassARRAY Assay Design 3.0 Software (San Diego, CA USA). PCR primers of selected SNPs were listed in Supplemental Table 1. In addition, we used Agena Typer 4.0 Software (San Diego, CA, USA) to manage and analyze data.

Statistical analysis. We conducted all statistical analysis using Microsoft Excel and SPSS version 21.0 software (SPSS, Chicago, IL, USA). Student's *t*-test and chi-square test were used to compare the differences in age and sex between glioma patients and healthy controls. The Hardy-Weinberg equilibrium (HWE) was checked for controls with Fisher's exact test. We assessed the association of *PPARD* and *PPARG* polymorphisms with glioma risk by calculating odd ratios (OR) and 95% confidence intervals (CI) using logistic regression. Multifactor dimensionality reduction (MDR, version 3.0.2) was used to analyze SNP-SNP interactions on glioma risk. Then, we plotted patient survival curves by the Kaplan-Meier method and log-rank test. The association of *PPARD* and *PPARG* polymorphisms with OS and progression free survival (PFS) of glioma patients was evaluated by calculating hazard ratios (HR) and 95%CI using univariate and multivariate analysis. In multivariable survival analysis, we assessed the associations of *PPARD* and *PPARG* polymorphisms with glioma prognosis adjusted by age, sex, WHO grade, surgery, radiotherapy and chemotherapy. All tests were two-sided, and $P < 0.05$ was regarded as statistical significance. Additionally, our results were adjusted for multiple comparison using false discovery rate (FDR) correction.

Results

Characteristics of study population. The characteristics of 568 glioma patients and 509 healthy controls were presented in Table 1. The mean ages of the cases and controls were 39.68 ± 16.96 and 41.32 ± 15.69 years old, respectively. No significant variation in age or sex was found between the two groups (age: $P = 0.102$, sex: $P = 1.000$). Among glioma patients, 438 (77%) people were astrocytoma. According to WHO grading standards, 35 (6%) patients were grade I, 320 (56%) patients were grade II, and others are in high-grade glioma (III + IV). In addition, surgery method, radiotherapy and chemotherapy of patients were shown in Table 1.

Association of *PPARD* and *PPARG* polymorphisms with glioma risk. In Table 2, *PPARD* and *PPARG* polymorphisms were accord with HWE in controls ($P > 0.05$).

HaploReg (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) predicted that PPARD and PPARG polymorphisms were related to the regulation of SiPhy cons, Promoter histone marks, Enhancer histone marks, DNAse, Motifs changed, GRASP QTL hits, NHGRI/EBI GWAS hits, Selected eQTL. After adjustment for age and sex, *PPARD* polymorphisms (rs2016520, rs67056409 and rs1053049) were significantly associated with glioma risk ($P < 0.05$). Rs2016520 and rs1053049 of *PPARD* had a decreased glioma risk in allele (rs2016520: OR = 0.82, 95%CI = 0.68–0.99, $P = 0.041$; rs1053049: OR = 0.78, 95%CI = 0.64–0.95, $P = 0.012$), dominant (rs2016520: OR = 0.78, 95%CI = 0.62–1.00, $P = 0.047$; rs1053049: OR = 0.75, 95%CI = 0.59–0.96, $P = 0.020$) and additive (rs2016520: OR = 0.81, 95%CI = 0.67–0.99, $P = 0.037$; rs1053049: OR = 0.78, 95%CI = 0.64–0.95, $P = 0.012$) models. We found that the allele distribution of rs67056409 were significantly different between cases and controls ($P = 0.046$), and subjects had lower risk of glioma in additive model (OR = 0.82, 95%CI = 0.67–0.99, $P = 0.041$). There were no significant association between glioma risk and other genetic polymorphisms (rs2206030, rs2920503, rs4073770 and rs1151988). However, FDR analysis revealed that the significant associations between genetic polymorphisms and glioma risk were not reliable.

Characteristics	Glioma patients (N = 568)	Healthy controls (N = 509)	*P*
Age	39.68 ± 16.96	41.32 ± 15.69	0.102
>40	296(52%)	241(47%)	
≤40	272(48%)	268(53%)	
Sex			1.000
Male	313(55%)	280(55%)	
Female	255(45%)	229(45%)	
Astrocytoma			
Yes	438(77%)		
No	130 (23%)		
WHO grade			
I	35(6%)		
II	320(56%)		
III	149(26%)		
IV	64(12%)		
Surgery			
STR & NTR	181 (32%)		
GTR	387 (68%)		
Radiotherapy			
No	59 (10%)		
Conformable radiotherapy	154 (27%)		
Gamma knife	355 (63%)		
Chemotherapy			
No	337 (59%)		
Yes-temodar	49 (9%)		
Yes-not temodar	182 (32%)		

Table 1. Comparison of glioma patients and controls by characteristics. WHO, World Health Organization; STR, sub-total resection; NTR, near-total resection; GTR, gross-total resection.

We further did stratification analysis of *PPARD* and *PPARG* polymorphisms with glioma risk (Tables 3 and 4). For the subjects older than 40 years old, rs2016520, rs67056409 and rs1053049 of *PPARD* significantly decreased risk of glioma in multiple models ($P < 0.05$). Rs1053049 had a strong relationship with decreased risk of glioma in the subgroup of male (allele: OR = 0.76, 95%CI = 0.59–0.99, $P = 0.041$; dominant: OR = 0.71, 95%CI = 0.51–0.98, $P = 0.040$; additive: OR = 0.76, 95%CI = 0.59–0.99, $P = 0.040$). Then, we divided glioma patients to astrocytoma and others, we found that rs2016520, rs67056409 and rs1053049 of *PPARD* were significantly associated astrocytoma risk compared with other glioma ($P < 0.05$). We also explored the effect of WHO grade on the relationship of genetic polymorphisms with glioma risk. The results showed *PPARG* rs2920503 was strongly related to higher risk of high-grade glioma (III + IV) in co-dominant (OR = 2.04, 95%CI = 1.13–3.68, $P = 0.018$) and recessive (OR = 2.03, 95%CI = 1.15–3.57, $P = 0.014$) models. After FDR correction, the protective effects of rs2016520, rs67056409 and rs1053049 on glioma risk were still significant among the individuals older than 40 years old (FDR- $P < 0.05$).

MDR analysis. We used MDR analysis to assess the impact of the interaction among seven SNPs. The results obtained from MDR analysis for one- to seven- locus modes were presented in Table 5. A seven-locus model including polymorphisms of *PPARD* (rs2016520, rs67056409, rs1053049 and rs2206030) and *PPARG* (rs2920503, rs4073770 and rs1151988) was the best model of SNP-SNP interaction for glioma risk (cross-validation consistency = 10/10, accuracy = 0.660, sensitivity = 0.751, specificity = 0.570, $P < 0.001$).

Clinical factors and glioma prognosis. After obtained follow-up data of glioma patients, we investigated the impact of clinical factors on glioma prognosis (OS and PFS). As shown in Table 6, surgery and chemotherapy had significant correlations with OS and PFS of glioma ($P < 0.05$, FDR- $P < 0.05$). The prognosis of patients had gross-total resection (GTR) was better than those had sub-total resection (STR) or near-total resection (NTR) (OS: Log-rank $P = 1.54E-07$, HR = 0.63, 95%CI = 0.53–0.77, $P = 1.88E-06$, FDR- $P = 1.32E-05$; PFS: Log-rank $P = 1.91E-09$, HR = 0.59, 95%CI = 0.49–0.71, $P = 6.78E-08$, FDR- $P = 4.75E-07$). Additionally, glioma patients who undergone chemotherapy lived longer than those not (OS: Log-rank $P = 1.38E-05$, HR = 0.69, 95%CI = 0.58–0.83, $P = 7.47E-05$, FDR- $P = 0.000261$; PFS: Log-rank $P = 0.005$, HR = 0.79, 95%CI = 0.66–0.95, $P = 0.011$, FDR- $P = 0.039$). There were no significantly associations between other clinical factors (sex, age, WHO grade and radiotherapy) and glioma prognosis ($P > 0.05$).

Association of *PPARD* and *PPARG* polymorphisms with glioma prognosis. Then, we assessed the association of *PPARD* (rs2016520, rs67056409, rs1053049 and rs2206030) and *PPARG* (rs2920503, rs4073770 and rs1151988) polymorphisms with glioma prognosis. In Supplemental Table 2, univariate analysis did not show a

Gene	SNP	Chr: position	HaploReg v4.1	Group	Genotype			Allele frequency		Model	OR(95%CI)	*P*	FDR-*P*
					AA	AB	BB	MAF (A)	HWE- *P*				
PPARD	rs2016520	6: 35378778	SiPhy cons, Promoter histone marks, Enhancer histone marks, DNAse, Motifs changed, GRASP QTL hits, Selected eQTL	case	31	217	317	0.247		Allele	0.82(0.68–0.99)	**0.041**	0.214
				control	37	217	255	0.286	0.385	Co-dominant	0.67(0.40–1.11)	0.123	0.323
											0.80(0.62–1.03)	0.085	0.275
										Dominant	0.78(0.62–1.00)	**0.047**	0.214
										Recessive	0.74(0.45–1.21)	0.231	0.404
										Additive	0.81(0.67–0.99)	**0.037**	0.214
PPARD	rs67056409	6: 35383699	Promoter histone marks, Enhancer histone marks, DNAse, Motifs changed, Selected eQTL	case	32	226	310	0.255		Allele	0.82(0.68–1.00)	**0.046**	0.214
				control	40	219	250	0.294	0.455	Co-dominant	0.64(0.39–1.06)	0.081	0.275
											0.83(0.65–1.07)	0.147	0.323
										Dominant	0.80(0.63–1.02)	0.072	0.275
										Recessive	0.70(0.43–1.13)	0.146	0.323
										Additive	0.82(0.67–0.99)	**0.041**	0.214
PPARD	rs1053049	6: 35395618	DNAse, Motifs changed, GRASP QTL hits, Selected eQTL	case	30	203	334	0.232		Allele	0.78(0.64–0.95)	**0.012**	0.214
				control	39	206	264	0.279	1.000	Co-dominant	0.60(0.37–1.00)	0.051	0.214
											0.78(0.60–1.00)	0.051	0.214
										Dominant	0.75(0.59–0.96)	**0.020**	0.214
										Recessive	0.67(0.41–1.10)	0.114	0.323
										Additive	0.78(0.64–0.95)	**0.012**	0.214
PPARD	rs2206030	6: 35404354	Enhancer histone marks, Motifs changed, NHGRI/EBI GWAS hits, Selected eQTL	case	126	291	151	0.478		Allele	1.08(0.91–1.28)	0.371	0.546
				control	106	255	148	0.459	0.929	Co-dominant	1.17(0.83–1.65)	0.382	0.546
											1.12(0.84–1.48)	0.436	0.573
										Dominant	1.13(0.87–1.48)	0.361	0.546
										Recessive	1.08(0.81–1.45)	0.587	0.685
										Additive	1.08(0.91–1.29)	0.365	0.546
PPARG	rs2920503	3: 12324230	Motifs changed	case	55	233	280	0.302		Allele	1.00(0.83–1.20)	0.985	0.986
				control	43	221	245	0.302	0.529	Co-dominant	1.12(0.72–1.73)	0.612	0.695
											0.92(0.72–1.19)	0.529	0.635
										Dominant	0.95(0.75–1.21)	0.702	0.776
										Recessive	1.16(0.76–1.77)	0.482	0.595
										Additive	1.00(0.83–1.20)	0.986	0.986
PPARG	rs4073770	3: 12368233	Enhancer histone marks, Motifs changed, Selected eQTL	case	60	265	243	0.339		Allele	0.99(0.83–1.19)	0.924	0.972
				control	69	209	231	0.341	0.061	Co-dominant	0.83(0.56–1.22)	0.339	0.546
											1.21(0.93–1.56)	0.152	0.323
										Dominant	1.11(0.87–1.41)	0.390	0.546
										Recessive	0.75(0.52–1.09)	0.132	0.323
										Additive	0.99(0.83–1.18)	0.925	0.971
PPARG	rs1151988	3: 12511512	Enhancer histone marks, Motifs changed, GRASP QTL hits, Selected eQTL	case	7	133	428	0.129		Allele	0.84(0.66–1.07)	0.162	0.324
				control	9	135	365	0.150	0.488	Co-dominant	0.66(0.24–1.80)	0.418	0.566
											0.84(0.64–1.11)	0.217	0.396
										Dominant	0.83(0.63–1.09)	0.175	0.334
										Recessive	0.69(0.26–1.87)	0.470	0.595
										Additive	0.83(0.65–1.07)	0.154	0.323

Table 2. Association of *PPARD* and *PPARG* polymorphisms with glioma risk. SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; FDR, false discovery rate. Bold values indicate statistical significance ($P < 0.05$).

strong relationship of *PPARD* and *PPARG* polymorphisms with glioma prognosis ($P > 0.05$). Moreover, we did not observe significantly association of *PPARD* and *PPARG* polymorphisms with OS and PFS of glioma patients ($P > 0.05$, Supplemental Table 3).

Discussion

In this case-control study, we examined the association of *PPARD* and *PPARG* polymorphisms with glioma risk and prognosis in the Chinese Han population. After FDR correction, we found that *PPARD* polymorphisms were significantly associated with glioma risk, and the effects were dependent on age ($P < 0.05$, FDR- $P < 0.05$). Moreover, surgery method and chemotherapy had strongly effects on glioma prognosis (Log-rank $P < 0.05$, $P < 0.05$, FDR- $P < 0.05$).

PPARs are involved in the regulation of metabolic homeostasis, whose activity are controlled by fatty acid ligands[34]. After activation, PPARs heterodimerize with retinoid X receptors (RXRs) to affect the expression of

Gene	SNP	Model	Age						Sex					
			>40			≤40			Male			Female		
			OR(95%CI)	*P*	FDR-*P*	OR(95%CI)	*P*	FDR-*P*	OR(95%CI)	*P*	FDR-*P*	OR(95%CI)	*P*	FDR-*P*
PPARD	rs2016520	Allele	0.66(0.50–0.88)	**0.004**	**0.034**	1.01(0.77–1.31)	0.964	0.970	0.82(0.64–1.06)	0.130	0.455	0.82(0.61–1.09)	0.170	0.476
		Co-dominant	0.48(0.22–1.06)	0.070	0.173	0.90(0.45–1.79)	0.765	0.970	0.78(0.4–1.51)	0.460	0.855	0.54(0.24–1.19)	0.124	0.476
			0.61(0.43–0.88)	**0.008**	**0.047**	1.08(0.75–1.55)	0.675	0.970	0.74(0.53–1.04)	0.084	0.370	0.89(0.61–1.29)	0.526	0.757
		Dominant	0.60(0.42–0.84)	**0.004**	**0.034**	1.05(0.74–1.49)	0.774	0.970	0.75(0.54–1.03)	0.079	0.370	0.83(0.58–1.19)	0.312	0.624
		Recessive	0.59(0.27–1.28)	0.179	0.376	0.87(0.45–1.69)	0.678	0.970	0.89(0.47–1.70)	0.730	0.902	0.56(0.26–1.23)	0.149	0.476
		Additive	0.65(0.48–0.87)	**0.004**	**0.034**	1.01(0.76–1.33)	0.955	0.970	0.81(0.62–1.06)	0.119	0.454	0.81(0.60–1.09)	0.164	0.476
PPARD	rs67056409	Allele	0.65(0.49–0.86)	**0.003**	**0.034**	1.03(0.80–1.34)	0.811	0.970	0.80(0.62–1.03)	0.088	0.370	0.85(0.64–1.14)	0.276	0.580
		Co-dominant	0.40(0.19–0.85)	**0.017**	0.071	0.99(0.5–1.96)	0.969	0.970	0.73(0.38–1.41)	0.347	0.855	0.54(0.25–1.16)	0.112	0.476
			0.67(0.46–0.96)	**0.027**	0.095	1.12(0.78–1.6)	0.544	0.970	0.73(0.52–1.02)	0.069	0.370	0.97(0.67–1.41)	0.883	0.883
		Dominant	0.62(0.44–0.88)	**0.007**	**0.047**	1.10(0.78–1.55)	0.596	0.970	0.73(0.53–1.01)	0.058	0.370	0.90(0.63–1.29)	0.562	0.757
		Recessive	0.47(0.22–0.98)	**0.045**	0.135	0.93(0.48–1.82)	0.842	0.970	0.84(0.45–1.59)	0.595	0.855	0.54(0.26–1.15)	0.111	0.476
		Additive	0.65(0.49–0.86)	**0.003**	**0.034**	1.05(0.79–1.39)	0.732	0.970	0.79(0.61–1.03)	0.082	0.370	0.85(0.63–1.13)	0.264	0.580
PPARD	rs1053049	Allele	0.68(0.51–0.91)	**0.009**	**0.047**	0.89(0.68–1.17)	0.407	0.970	0.76(0.59–0.99)	**0.041**	0.370	0.80(0.60–1.08)	0.143	0.476
		Co-dominant	0.41(0.18–0.93)	**0.033**	0.107	0.80(0.41–1.57)	0.518	0.970	0.63(0.33–1.21)	0.163	0.527	0.56(0.25–1.25)	0.159	0.476
			0.71(0.50–1.03)	0.069	0.173	0.88(0.61–1.26)	0.473	0.970	0.73(0.52–1.02)	0.065	0.370	0.85(0.58–1.23)	0.385	0.703
		Dominant	0.67(0.47–0.95)	**0.024**	0.092	0.86(0.61–1.22)	0.406	0.970	0.71(0.51–0.98)	**0.040**	0.370	0.80(0.56–1.15)	0.232	0.573
		Recessive	0.47(0.21–1.05)	0.065	0.173	0.85(0.44–1.63)	0.625	0.970	0.72(0.39–1.36)	0.315	0.855	0.60(0.27–1.32)	0.204	0.536
		Additive	0.68(0.51–0.91)	**0.010**	**0.047**	0.89(0.67–1.17)	0.389	0.970	0.76(0.59–0.99)	**0.040**	0.370	0.80(0.59–1.08)	0.142	0.476
PPARD	rs2206030	Allele	1.04(0.82–1.33)	0.726	0.828	1.10(0.86–1.40)	0.446	0.970	1.09(0.87–1.37)	0.460	0.855	1.07(0.83–1.38)	0.605	0.757
		Co-dominant	1.11(0.68–1.81)	0.683	0.820	1.25(0.75–2.07)	0.391	0.970	1.19(0.74–1.91)	0.471	0.855	1.14(0.69–1.89)	0.613	0.757
			1.29(0.85–1.96)	0.232	0.424	0.97(0.65–1.44)	0.866	0.970	1.13(0.78–1.65)	0.516	0.855	1.10(0.72–1.69)	0.659	0.762
		Dominant	1.23(0.83–1.83)	0.304	0.532	1.04(0.71–1.51)	0.848	0.970	1.15(0.80–1.64)	0.448	0.855	1.11(0.74–1.67)	0.602	0.757
		Recessive	0.93(0.62–1.40)	0.735	0.828	1.27(0.82–1.98)	0.280	0.970	1.10(0.73–1.64)	0.653	0.885	1.07(0.70–1.63)	0.753	0.791
		Additive	1.06(0.83–1.35)	0.665	0.820	1.10(0.86–1.41)	0.459	0.970	1.09(0.87–1.38)	0.450	0.855	1.07(0.83–1.38)	0.606	0.757
PPARG	rs2920503	Allele	1.00(0.77–1.30)	0.996	0.996	1.01(0.78–1.30)	0.970	0.970	1.05(0.82–1.34)	0.717	0.902	0.95(0.72–1.25)	0.705	0.762
		Co-dominant	1.15(0.61–2.17)	0.671	0.820	1.07(0.57–1.98)	0.840	0.970	1.18(0.65–2.14)	0.583	0.855	1.05(0.55–2.00)	0.878	0.883
			0.91(0.64–1.30)	0.604	0.794	0.91(0.63–1.31)	0.612	0.970	0.99(0.71–1.39)	0.971	0.971	0.84(0.58–1.23)	0.368	0.703
		Dominant	0.95(0.67–1.33)	0.749	0.828	0.94(0.66–1.33)	0.710	0.970	1.02(0.74–1.41)	0.891	0.959	0.88(0.61–1.25)	0.469	0.757
		Recessive	1.20(0.65–2.22)	0.561	0.794	1.11(0.61–2.02)	0.722	0.970	1.18(0.67–2.09)	0.561	0.855	1.14(0.61–2.11)	0.685	0.762
		Additive	1.00(0.77–1.31)	0.996	0.996	0.98(0.75–1.28)	0.900	0.970	1.05(0.82–1.35)	0.715	0.902	0.95(0.72–1.25)	0.708	0.762
PPARG	rs4073770	Allele	0.94(0.73–1.21)	0.605	0.794	1.05(0.82–1.35)	0.689	0.970	1.07(0.84–1.37)	0.573	0.855	0.90(0.69–1.18)	0.449	0.757
		Co-dominant	0.79(0.45–1.40)	0.414	0.669	0.86(0.50–1.50)	0.599	0.970	1.05(0.62–1.80)	0.848	0.960	0.63(0.35–1.12)	0.118	0.476
			1.02(0.71–1.46)	0.930	0.976	1.40(0.97–2.04)	0.076	0.970	1.17(0.83–1.65)	0.371	0.855	1.25(0.85–1.83)	0.256	0.580
		Dominant	0.97(0.68–1.36)	0.843	0.908	1.25(0.88–1.78)	0.206	0.970	1.14(0.83–1.58)	0.415	0.855	1.07(0.75–1.54)	0.704	0.762
		Recessive	0.78(0.46–1.34)	0.372	0.625	0.73(0.43–1.23)	0.237	0.970	0.98(0.59–1.62)	0.925	0.971	0.56(0.33–0.97)	0.038	0.476
		Additive	0.93(0.72–1.20)	0.569	0.794	1.04(0.81–1.34)	0.736	0.970	1.07(0.84–1.36)	0.575	0.855	0.91(0.70–1.18)	0.455	0.757
PPARG	rs1151988	Allele	0.78(0.54–1.12)	0.170	0.376	0.91(0.66–1.28)	0.599	0.970	0.96(0.69–1.33)	0.799	0.932	0.72(0.50–1.03)	0.074	0.476
		Co-dominant	0.52(0.09–3.20)	0.482	0.750	0.80(0.23–2.75)	0.723	0.970	0.71(0.19–2.68)	0.610	0.855	0.61(0.13–2.76)	0.520	0.757
			0.78(0.52–1.17)	0.224	0.424	0.91(0.61–1.35)	0.645	0.970	0.99(0.68–1.45)	0.969	0.971	0.69(0.46–1.04)	0.076	0.476
		Dominant	0.77(0.52–1.14)	0.191	0.382	0.9(0.62–1.33)	0.602	0.970	0.97(0.67–1.41)	0.885	0.960	0.68(0.46–1.02)	0.065	0.476
		Recessive	0.55(0.09–3.38)	0.523	0.785	0.82(0.24–2.81)	0.751	0.970	0.71(0.19–2.68)	0.611	0.855	0.67(0.15–3.03)	0.602	0.757
		Additive	0.77(0.53–1.12)	0.171	0.376	0.91(0.64–1.28)	0.577	0.970	0.96(0.68–1.34)	0.793	0.932	0.71(0.49–1.03)	0.068	0.476

Table 3. Association of *PPARD* and *PPARG* polymorphisms with glioma risk stratified by age and sex. SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; FDR, false discovery rate. Bold values indicate statistical significance ($P < 0.05$).

downstream genes. It is reported that PPARs might had a functional crosstalk concerning the control of their expression[35]. Previous studies on the role of PPARs signaling in cancer mainly based on the availability of PPARs agonists and antagonists[36]. In brain tumor stem cells, PPARγ agonists inhibit cell growth and induce cell cycle arrest[37]. In mice, expression of PPARδ is related to prognosis and metastatic ability of breast cancer cells[38]. Polymorphisms of *PPARD* and *PPARG* are associated with risk and prognosis of many diseases, including cardiovascular disease, diabetes, brain diseases, medulloblastoma and other cancers[39–41]. In our study, we firstly observed that *PPARD* polymorphisms (rs2016520, rs67056409 and rs1053049) were significantly associated with glioma risk. Similar association has been reported in colorectal cancer[39]. It suggests that *PPARD* polymorphisms could be involved in the susceptibility of glioma development. And, stratified analysis showed the effects

Gene	SNP	Model	Astrocytoma VS. Other glioma			WHO grade (III + IV VS. I + II)		
			OR(95%CI)	*P*	FDR- *P*	OR(95%CI)	*P*	FDR- *P*
PPARD	rs2016520	Allele	0.79(0.64–0.97)	**0.025**	0.224	0.97(0.73–1.28)	0.810	0.989
		Co-dominant	0.60(0.34–1.05)	0.072	0.236	1.08(0.50–2.33)	0.844	0.989
			0.80(0.61–1.05)	0.103	0.254	0.98(0.68–1.41)	0.923	0.992
		Dominant	0.77(0.60–1.00)	**0.048**	0.224	0.99(0.70–1.41)	0.973	0.992
		Recessive	0.66(0.38–1.14)	0.135	0.315	1.09(0.51–2.32)	0.826	0.989
		Additive	0.79(0.64–0.97)	**0.027**	0.224	1.01(0.76–1.35)	0.956	0.992
PPARD	rs67056409	Allele	0.80(0.65–0.98)	**0.033**	0.224	0.93(0.70–1.22)	0.598	0.989
		Co-dominant	0.58(0.34–1.01)	0.054	0.227	0.80(0.36–1.77)	0.584	0.989
			0.84(0.64–1.10)	0.198	0.362	1.03(0.72–1.48)	0.863	0.989
		Dominant	0.80(0.62–1.03)	0.089	0.239	1.00(0.71–1.42)	0.992	0.992
		Recessive	0.63(0.37–1.08)	0.091	0.239	0.79(0.36–1.72)	0.554	0.989
		Additive	0.80(0.65–0.99)	**0.039**	0.224	0.97(0.73–1.29)	0.828	0.989
PPARD	rs1053049	Allele	0.76(0.61–0.93)	**0.009**	0.224	0.92(0.69–1.23)	0.581	0.989
		Co-dominant	0.56(0.32–0.98)	**0.043**	0.224	0.87(0.39–1.95)	0.744	0.989
			0.77(0.59–1.02)	0.064	0.236	0.97(0.67–1.40)	0.871	0.989
		Dominant	0.74(0.57–0.96)	**0.024**	0.224	0.96(0.67–1.36)	0.810	0.989
		Recessive	0.62(0.36–1.08)	0.091	0.239	0.89(0.40–1.95)	0.762	0.989
		Additive	0.76(0.62–0.94)	**0.012**	0.224	0.95(0.71–1.28)	0.754	0.989
PPARD	rs2206030	Allele	1.09(0.91–1.31)	0.342	0.497	1.08(0.85–1.38)	0.510	0.989
		Co-dominant	1.18(0.82–1.70)	0.376	0.497	1.14(0.69–1.88)	0.615	0.989
			1.09(0.81–1.48)	0.572	0.632	1.38(0.91–2.10)	0.131	0.523
		Dominant	1.12(0.84–1.49)	0.447	0.539	1.30(0.88–1.94)	0.192	0.620
		Recessive	1.12(0.82–1.52)	0.489	0.555	0.92(0.61–1.39)	0.684	0.989
		Additive	1.09(0.91–1.30)	0.372	0.497	1.08(0.84–1.38)	0.560	0.989
PPARG	rs2920503	Allele	0.91(0.75–1.12)	0.379	0.497	1.27(0.98–1.64)	0.074	0.499
		Co-dominant	0.92(0.57–1.49)	0.744	0.801	2.04(1.13–3.68)	**0.018**	0.378
			0.85(0.65–1.11)	0.235	0.386	1.02(0.70–1.47)	0.933	0.992
		Dominant	0.86(0.67–1.11)	0.255	0.397	1.17(0.83–1.65)	0.377	0.989
		Recessive	0.99(0.63–1.58)	0.982	0.982	2.03(1.15–3.57)	**0.014**	0.378
		Additive	0.91(0.75–1.12)	0.370	0.497	1.27(0.98–1.64)	0.074	0.499
PPARG	rs4073770	Allele	1.02(0.85–1.24)	0.818	0.838	0.80(0.62–1.03)	0.083	0.499
		Co-dominant	0.86(0.56–1.31)	0.480	0.555	0.70(0.38–1.27)	0.240	0.672
			1.28(0.98–1.69)	0.073	0.236	0.73(0.51–1.06)	0.095	0.499
		Dominant	1.18(0.91–1.53)	0.211	0.369	0.73(0.51–1.03)	0.071	0.499
		Recessive	0.76(0.51–1.13)	0.170	0.340	0.82(0.46–1.45)	0.489	0.989
		Additive	1.03(0.85–1.24)	0.799	0.838	0.80(0.61–1.04)	0.092	0.499
PPARG	rs1151988	Allele	0.83(0.64–1.08)	0.160	0.340	1.25(0.88–1.78)	0.209	0.627
		Co-dominant	0.62(0.21–1.88)	0.403	0.513	1.54(0.34–7.05)	0.580	0.989
			0.84(0.62–1.13)	0.239	0.386	1.34(0.90–2.00)	0.154	0.539
		Dominant	0.82(0.61–1.10)	0.191	0.362	1.35(0.91–2.00)	0.137	0.523
		Recessive	0.65(0.22–1.97)	0.449	0.539	1.43(0.31–6.52)	0.646	0.989
		Additive	0.83(0.63–1.08)	0.164	0.340	1.32(0.92–1.90)	0.137	0.523

Table 4. Association of *PPARD* and *PPARG* polymorphisms with glioma risk stratified by pathological classification and WHO grade. SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; FDR, false discovery rate. Bold values indicate statistical significance ($P < 0.05$).

of *PPARD* polymorphisms on glioma risk were age-dependent. It provides a scientific basis on individualized treatment of glioma. The effects of *PPARD* polymorphisms on glioma risk might related to SiPhy cons, Promoter histone marks, Enhancer histone marks, DNAse, Motifs changed, GRASP QTL hits, NHGRI/EBI GWAS hits, Selected eQTL. However, our results should be confirmed in further studies, including next-generation technology, PCR, western-blot analysis, etc.

Glioma is likely to have unfavorable prognosis caused by rapid proliferation and diffuse brain invasion. Despite surgery, chemotherapy and radiotherapy treatments improve, the prognosis of glioma remains poor[42]. Recent studies reported that some lipophilic molecules have antiproliferation and/or differentiation effects on glioma cells, and PPARs mediated some activities of these processes[43]. PPARγ has been observed in transformed neural cells of human and PPARγ agonist interferes with glioma growth and malignancy[43–45]. In this study, we

Model	Bal. Acc. CV Training	Bal. Acc. CV Testing	CV Consistency	Accuracy	Sensitivity	Specificity	OR(95%CI)	*P*
rs1053049	0.538	0.513	8/10	0.537	0.593	0.481	1.35(1.06–1.74)	**0.017**
rs1053049, rs2206030	0.554	0.512	5/10	0.550	0.646	0.454	1.52(1.18–1.95)	**0.001**
rs2920503, rs1053049, rs2206030	0.573	0.471	2/10	0.566	0.554	0.578	1.70(1.33–2.18)	<**0.001**
rs2920503, rs4073770, rs2016520, rs2206030	0.602	0.500	7/10	0.597	0.646	0.548	2.22(1.72–2.85)	<**0.001**
rs2920503, rs4073770, rs1151988, rs2016520, rs2206030	0.630	0.500	5/10	0.624	0.601	0.646	2.76(2.14–3.55)	<**0.001**
rs2920503, rs4073770, rs1151988, rs67056409, rs1053049, rs2206030	0.658	0.506	10/10	0.650	0.751	0.550	3.68(2.82–4.80)	<**0.001**
rs2920503, rs4073770, rs1151988, rs2016520, rs67056409, rs1053049, rs2206030	0.668	0.4951	10/10	0.660	0.751	0.570	3.98(3.05–5.20)	<**0.001**

Table 5. MDR analysis of SNP-SNP interaction. MDR, multifactor dimensionality reduction; SNP, single nucleotide polymorphism; CV, cross-validation; OR, odds ratio; CI, confidence interval. Bold values indicate statistical significance ($P < 0.05$).

Variables		Total	Event	OS				PFS					
				Log-rank *P*	SR (1-/3-year)	HR (95%CI)	*P*	FDR- *P*	Log-rank *P*	SR (1-/3-year)	HR (95%CI)	*P*	FDR- *P*
Sex	Male	313	278	0.379	0.328/0.082	1.08 (0.92–1.28)	0.420	0.490	0.268	0.200/0.096	1.09 (0.92–1.30)	0.321	0.321
	Female	255	229		0.310/0.094					0.155/0.089			
Age	<40	250	215	0.074	0.355/0.117	1.16 (0.97–1.38)	0.101	0.235	0.064	0.206/0.119	1.16 (0.97–1.38)	0.097	0.136
	≥40	317	291		0.290/0.067					0.159/0.072			
WHO grade	I + II	355	311	0.121	0.328/0.108	1.14 (0.95–1.36)	0.155	0.271	0.096	0.192/0.108	1.15 (0.96–1.37)	0.136	0.159
	III + IV	213	196		0.305/0.064					0.158/0.067			
Surgery	NTR & STR	181	178	**1.54E-07**	0.204/—	**0.63 (0.53–0.77)**	**1.88E-06**	**1.32E-05**	**1.91E-09**	0.016/—	**0.59 (0.49–0.71)**	**6.78E-08**	**4.75E-07**
	GTR	387	329		0.374/0.123					0.254/0.126			
Radiotherapy	No	59	48	0.438	0.441/—				0.118	0.200/—			0.136
Conformal radiotherapy		154	126		0.250/0.152	1.08 (0.78–1.51)	0.636	0.636		0.217/0.154	1.37 (0.97–1.94)	0.070	
	Gamma knife	355	333		0.330/0.055	1.17 (0.87–1.59)	0.303	0.424		0.163/0.058	1.31 (0.96–1.80)	0.090	0.136
Chemotherapy	No	337	315	**1.38358E-05**	0.276/0.029	**0.69 (0.58–0.83)**	**7.46734E-05**	**0.000261**	**0.005**	0.164/0.057	**0.79 (0.66–0.95)**	**0.011**	**0.039**
	Yes	231	192		0.384/0.151					0.205/0.155			

Table 6. The impact of clinical factors on glioma patient OS and PFS. OS, overall survival; PFS, progression free survival; SR, survival rate; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; STR, sub-total resection; NTR, near-total resection; GTR, gross-total resection; FDR, false discovery rate. Bold values indicate statistical significance ($P < 0.05$).

firstly confirmed the effects of surgery method and chemotherapy on prognosis of glioma patients. Then, we explored the association of *PPARD* and *PPARG* polymorphisms with OS and PFS of glioma patients. No significant associations were observed by univariate and multivariate analysis. It demonstrated that *PPARD* and *PPARG* polymorphisms might not contribute the prognosis of glioma.

There are some limitations in the present study. First, we selected and genotyped several polymorphisms of *PPARD* and *PPARG*, more genetic polymorphisms should be studied in the future. Second, we could not evaluate more factors on the association of genetic polymorphisms and glioma risk due to the limited sample size and information. Third, the molecular mechanisms of *PPARD* and *PPARG* on glioma risk and prognosis are not elucidated in our study.

Conclusion

In conclusion, we found genetic polymorphisms of *PPARD* were associated with glioma risk in the Chinese Han population, which suggests the role of *PPARD* in the carcinogenesis of glioma.

It provided information on exploring the mechanism and targeted therapy of glioma, it also promotes the development of precision medicine on glioma. Further studies in larger samples with more ethnic groups are needed to validate our results and explore the mechanism of *PPARD* and *PPARG* in glioma.

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Author contributions
Xiaoying Ding and Ya Gao designed this study, Xinsheng Han and Haozheng Yuan collected samples, Yong Zhang wrote the manuscript, Ya Gao revised the draft and supervised this study.

Competing interests
The authors declare no competing interests.

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