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Increased *HSPG2* expression independently predicts poor survival in patients with oligoastrocytoma and oligodendroglioma

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Abstract. – OBJECTIVE: Perlecan, which is also called heparan sulfate proteoglycan 2 (HSPG2), is a protein encoded by the HSPG2 gene that maps to 1p36.12 in the human genome. In this study, we assessed the independent prognostic value of HSPG2 in terms of overall survival (OS) and recurrence-free survival (RFS) in patients with LGG.

PATIENTS AND METHODS: A retrospective study was conducted by using data in the Cancer Genome Atlas-Low Grade Glioma (TCGA-LGG).

RESULTS: Increased HSPG2 expression was an independent prognostic indicator of poor OS in oligoastrocytoma (HR: 1.644, 95% CI: 1.116-2.423, $p = 0.012$) and in oligodendroglioma (HR: 1.459, 95% CI: 1.138-1.871, $p = 0.003$). In addition, increased HSPG2 expression independently predicted poor RFS in oligodendroglioma (HR: 1.402, 95% CI: 1.110-1.770, $p = 0.005$). Furthermore, we observed that high HSPG2 expression was associated with significantly shorter OS and RFS in oligodendroglioma, no matter the patients received radiotherapy or not. Using copy number alterations (CNAs) and DNA methylation data in TCGA-LGG, we found that DNA copy deletion was generally associated with decreased HSPG2 expression. Regression analysis suggested a weak negative correlation between HSPG2 expression and HSPG2 DNA methylation (Pearson's r = -0.388).

CONCLUSIONS: Increased HSPG2 expression could independently predict poor OS in oligoastrocytoma and oligodendroglioma and also independently predicted poor RFS in oligodendroglioma. Its expression is modulated by both DNA copy number and DNA methylation in oligodendroglioma.

Key Words:
HSPG2, Oligodendrogliomas, Overall survival, Recurrence-free survival, Radiotherapy.

Introduction

World Health Organization (WHO) grade II gliomas, (Low-grade gliomas, LGG) is a set of biologically diverse neoplasms that usually include astrocytoma, oligoastrocytoma and oligodendroglioma[1]. Previous studies have attempted to identify prognostic factors for LGG, such as age > 40 years, astrocytoma histology, large tumor diameters and tumor crossing the midline[2]. Some molecular markers have also been proposed as potential predictors of survival outcome, such has 1p/19q co-deletion[3] and isocitrate dehydrogenase 1 and 2 genes (IDH1/2) mutation[1]. However, the clinical relevance of the molecular markers is still controversial[4,5]. For example, 1p/19q deletion is associated with sensitivity to alkylating agent chemotherapy and radiotherapy in oligodendroglioma[6]. However, the 1p/19q deletion loses its prognostic value in patients with oligodendroglioma who receive no further radiotherapy or chemotherapy after surgery[7], limiting 1p/19q deletion as a candidate predictive marker for prolonged survival in response to DNA-damaging treatments[7]. Therefore, it is meaningful to explore other specific genetic markers to predict prognosis in histological subtypes of LGG. Perlecan, which is also called heparan sulfate proteoglycan 2 (HSPG2), is a protein encoded by the HSPG2 gene (maps to 1p36.12 in the human genome)[8]. In fact, 1p36 is a Carcinoma Prostate Brain (CAPB) locus that hosts a series of oncogene for these tumors[9]. Functionally, HSPG2 is one of the major components of the vascular extracellular matrix and basement membranes[10]. As a large multidomain proteoglycan, HSPG2 binds to and cross-links many

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extracellular matrix components and cell-surface molecules, such as laminin, prolargin, collagen type IV, FGFBP1, FBLN2, FGF7 and transthyretin, thereby helping to maintain vascular homeostasis and endothelial barrier function[11,12]. Some recent studies found that deregulated HSPG2 is associated with malignant behaviors of some cancers. High HSPG2 expression might be an indicator of prostate cancer grade, invasion potential and distant metastasis[13,14]. In brain metastases of lung cancer and melanoma, HSPG2 has over 50 folds increase compared with epilepsy control [15]. Since HSPG2 locates in 1p36, it might be a potential prognosis related gene in LGG. In this study, we studied the independent prognostic value of HSPG2 expression in terms of overall survival (OS) and recurrence-free survival (RFS) in each subtype of LGG and also investigated the possible mechanisms of its dysregulation.

Patients and Methods

Data Mining in the Cancer Genome Atlas (TCGA)-LGG

The level-3 data of TCGA-LGG were downloaded by using the UCSC Xena (https://xenabrowser.net/). In this cohort, 517 patients with primary LGG were included, while 511 among them had intact OS data recorded. This part of patients was included in survival analysis in this study. Their clinicopathological parameters, including HSPG2 expression (measured by RNA-seq), age at initial diagnosis, gender, histological subtypes, Karnofsky Performance Score (KPS), IDH1 mutation, O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, the history of targeted molecular therapy/radiation therapy, OS status, OS in days, RFS status and RFS in days, were downloaded using UCSC Xena Browser (http://xena.ucsc.edu/), a bioinformatics tool to visualize functional genomics data from multiple sources, including TCGA data. The HSPG2 DNA methylation data (measured by Illumina 450k infinium methylation beadchip) (Illumina, San Diego, CA, USA) and the gene-level thresholded GISTIC2-processed Copy number alterations (CNAs) data were downloaded by using UCSC Xena Browser. A previous work reported 18 CpG sites in the promoter of MGMT [16], among which 14 were covered in the beadchip. The average methylation value of the 14 CpG sites was calculated to represent the methylation status of the MGMT promoter. The correlation between HSPG2 expression and its DNA methylation was analyzed using cBioPortal for Cancer Genomics (http://www.cbioportal.org/). This study was approved by the Ethics Committee of Tsinghua University, China.

Statistical Analysis

HSPG2 expression in different groups was compared using one-way ANOVA followed by Tukey's post-hoc test or using Welch's *t*-test. Receiver operating characteristic (ROC) analysis for death and recurrence detection was performed to determine the optional cutoff (Youden index) for HSPG2 expression. The association between HSPG2 RNA expression and the clinicopathological features between the groups with high/low HSPG2 expression was assessed by using χ^2-tests. Kaplan-Meier curves showing the association between *HSPG2/ALPL* RNA expression and OS/RFS were generated by using GraphPad Prism 6.0 (GraphPad Prism Inc., La Jolla, CA, USA). Log-rank test was used to assess the significance of the difference between the Kaplan-Meier survival curves. Univariate and multivariate Cox regression models were used to assess prognostic significance. Regression analysis was performed to determine the correlation between *HSPG2* RNA expression and its DNA methylation. $p < 0.05$ was considered statistically significant.

Results

High HSPG2 Expression is an Independent Predictor of OS in Patients with Oligoastrocytoma and Oligodendroglioma

The patients with LGG were divided into high and low HSPG2 groups according to the Youden Index in ROC analysis of OS. The clinicopathological features in LGG patients with high (N = 255) and low (N = 256) HSPG2 expression were summarized and compared in Table I. High HSPG2 expression was associated with a significantly lower ratio of IDH1 mutation (164/255 *vs.* 232/256, $p < 0.001$) and a lower level of MGMT promoter methylation (0.39±0.13 *vs.* 0.43±0.11, $p < 0.001$) (Table I), but was associated with a substantially higher proportion of astrocytoma (119/255 *vs.* 74/256, $p < 0.001$), recurrence (85/209 *vs.* 46/218, $p < 0.001$) and death (94/255 *vs.* 31/256, $p < 0.001$) compared to the low HSPG2 expression group (Table I). Using survival data in TCGA-LGG, we assessed the association between HSPG2 expression and OS in patients with LGG by generating

Kaplan-Meier survival curves. Results showed that high HSPG2 expression was generally associated with shorter OS ($p < 0.001$) (Figure 1A). Subgroup analysis showed that the association was more evident in oligodendroglioma (Log-rank $\chi^2 = 25.99$, $p < 0.001$) (Figure 1D) than in astrocytoma (Log-rank $\chi^2 = 12.20$, $p < 0.001$) and in oligoastrocytoma (Log-rank $\chi^2 = 9.63$, $p = 0.002$) (Figure 1B-C). In univariate analysis, older age (≥42), astrocytoma, low KPS score (≤80), no IDH1 mutation, lower level of MGMT promoter methylation, with radiation therapy and increased HSPG2 expression were associated with shorter OS (Table II). Multivariate analysis showed older age (≥ 42), astrocytoma, low KPS score (≤ 80) and no IDH1 mutations were independent prognostic factors of poor OS in LGG (Table II). However, HSPG2 expression had no independent prognostic value in the mixture of histological subtypes (HR: 1.116, 95% CI: 0.966-1.288, $p = 0.136$) (Table II). Actually, the three subtypes of LGG (oligodendroglioma, astrocytoma and oligoastrocytoma) have significant heterogeneity in molecular mechanisms and have different prognostic implications. Then, we performed subgroup analysis in these three subtypes. Results showed that HSPG2 was not an independent marker in astrocytoma, but independently predicted poor OS in oligoastrocytoma (HR: 1.644, 95% CI: 1.116-2.423, $p = 0.012$) and in oligodendroglioma (HR: 1.459, 95%CI: 1.138-1.871, $p = 0.003$) (Table III).

High HSPG2 Expression Is an Independent Predictor of RFS in Patients with Oligodendroglioma

Then, we assessed the association between HSPG2 expression and RFS. Log-rank test indicated that high HSPG2 expression was generally associated with shorter RFS ($p < 0.001$) (Figure 2A). Kaplan-Meier curves in each subgroup analysis also confirmed the associations (Figure 2B-D). In univariate analysis, older age (≥ 42), low KPS score (≤ 80), no IDH1 mutation, lower level of MGMT promoter methylation, with targeted molecular therapy and increased HSPG2 expression were associated with unfavorable RFS (Table IV). Multivariate analysis showed older age (≥ 42), low KPS score (≤ 80), no IDH1 mutation and lower

Table I. Demographic and clinicopathological parameters of patients with primary LGG in TCGA-LGG.

		HSPG2 expression RNAseq			
Parameters		**High (N = 255)**	**Low (N = 256)**	χ^2	***p*-value**
Age (Mean ± SD)		44.85±14.25	41.19±12.17		**0.002**
Gender	Female	123	105	2.67	0.10
	Male	132	151		
Subtypes	Astrocytoma	119	74	17.28	**< 0.001**
	Oligoastrocytoma	54	76		
	Oligodendroglioma	82	106		
KPS	≤ 80	61	42	2.85	0.092
	> 80	97	101		
	No data	97	113		
IDH1 mutation	No	91	24	50.71	**< 0.001**
	Yes	164	232		
MGMT promoter methylation (Mean ± SD)		0.39 ± 0.13	0.43 ± 0.11		**< 0.001**
Targeted molecular therapy	Yes	151	113	16.24	**< 0.001**
	No	74	120		
	Discrepancy/no data	30	23		
Radiation therapy	Yes	160	128	11.24	**< 0.001**
	No	70	107		
	Discrepancy/no data	25	21		
Recurrence status	No	124	172	19.21	**< 0.001**
	Yes	85	46		
	Null	46	38		
Living status	Living	161	225	42.36	**< 0.001**
	Dead	94	3		

KPS: Karnofsky Performance Score.

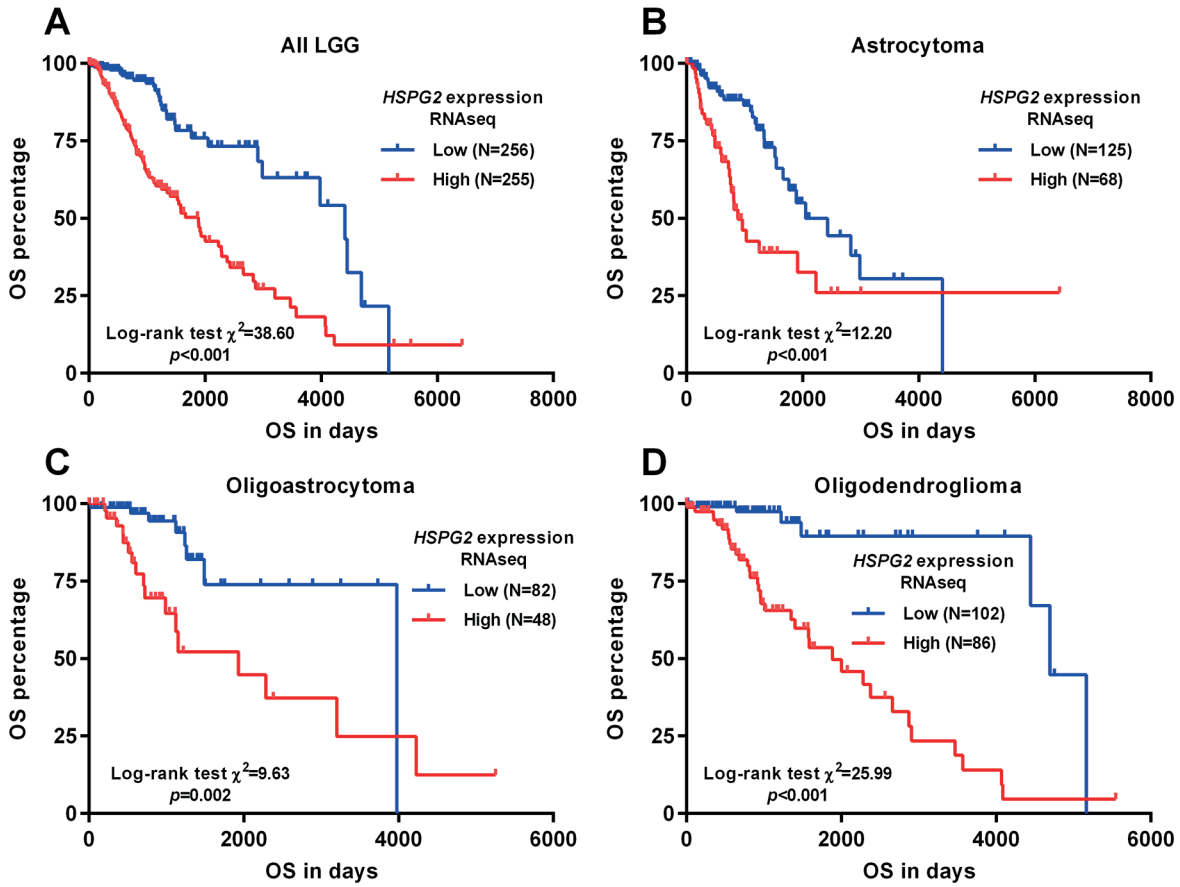

Figure 1. The association between HSPG2 expression and OS in different subgroups of LGG. ***A-D***. The Kaplan-Meier curves of OS in LGG ***(A)***, astrocytoma ***(B)***, oligoastrocytoma ***(C)*** and oligodendroglioma ***(D)***. Patients were divided into two groups according to the best cutoff of HSPG2 expression. Data were from TCGA-LGG. Log-rank test was performed to assess the significance of the difference.

Table II. Univariate and multivariate analyses of OS in patients with primary LGG in TCGA-LGG.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95%CI**	***p***	**HR**	**95% CI**	***p***
Age						
≥ 42 vs. < 42	3.391	2.292-5.018	**< 0.001**	3.058	1.996-4.683	**< 0.001**
Gender						
Female vs. Male	0.915	0.642-1.306	0.626			
Subtypes						
Oligodendroglioma	1.000					
Astrocytoma	1.785	1.195-2.667	**0.005**	1.949	1.282-2.963	**0.002**
Oligoastrocytoma	1.080	0.657-1.777	0.761			
KPS						
≤ 80 vs. > 80	2.435	1.599-3.708	**< 0.001**	1.862	1.197-2.899	**0.006**
IDH1 mutation						
No vs. Yes	4.251	2.962-6.101	**< 0.001**	2.725	1.675-4.433	**< 0.001**
MGMT promoter methylation						
(Continuous)	0.050	0.011-0.240	**< 0.001**	0.656	0.121-3.551	0.624
Targeted molecular therapy						
Yes vs. No	1.348	0.912-1.992	0.134			
Radiation therapy						
Yes vs. No	1.971	1.264-3.074	**0.003**	1.126	0.687-1.846	0.637
***HSPG2* expression** (Continuous)	1.394	1.247-1.559	**< 0.001**	1.116	0.966-1.288	0.136

level of MGMT promoter methylation were independent prognostic factors of poor RFS in LGG (Table IV). However, in the following subgroup analysis, we found that HSPG2 had independent prognostic value in terms of RFS in oligodendroglioma (HR=1.402, 95% CI: 1.110-1.770, p = 0.005) (Table V).

High HSPG2 Expression is Associated With Poor Survival in Patients with Oligodendroglioma Regardless of Radiotherapy

Since HSPG2 locates in 1p36, 1p/19q co-deletion in oligodendroglioma might reduce the importance of this potential prognostic marker. To verify the specific prognostic value of HSPG2, we identified another gene-ALPL, which is also located in 1p36 (Figure 3A) and compared its association with survival outcomes in oligodendroglioma. Kaplan-Meier curves showed that under the best cutoff model, ALPL expression was not an unfavorable, but a favorable prognostic marker in terms of OS (p < 0.001) and RFS (p = 0.007) (Figure 3B-C). Therefore, we infer that the genes in 1p/19q might have different prognostic value. In addition, since 1p/19q deletion loses its prognostic value of in oligodendroglioma without DNA-damaging treatments[7], we also tried to assess the independent prognostic value of HSPG2 in oligodendroglioma patients with or without radiotherapy. Kaplan-Meier curves of survival showed that high HSPG2 expression was associated with significantly shorter OS and RFS, no matter the patients received radiotherapy or not (Figure 4A-D).

HSPG2 Expression is Modulated by DNA Copy Number and DNA Methylation in Oligodendroglioma

Then, we tried to explore the mechanism underlying HSPG2 dysregulation. Since 1p deletion was common in oligodendroglioma, we first examined the association between copy number alterations and HSPG2 RNA expression in LGG. Heatmap showed that DNA copy deletion was generally associated with decreased HSPG2 expression (Figure 5A). In addition, oligodendroglioma has a higher ratio of HSPG2 shallow deletion than astrocytoma and oligoastrocytoma (Figure 5A-B). However, in the heatmap, we also observed that HSPG2 expression was not consistent in oligodendroglioma with HSPG2 DNA shallow deletion (Figure 5A,

Table III. Univariate and multivariate analyses of OS in patients with different subtypes of LGG in TCGA-LGG.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***p***	**HR**	**95%CI**	***p***
Astrocytoma						
Age						
≥ 42 vs. < 42	3.914	2.249-6.812	**< 0.001**	2.332	1.233-4.411	**0.009**
KPS						
≤ 80 vs. > 80	2.619	1.419-4.831	**0.002**	1.908	1.007-3.614	**0.047**
***IDH1* mutation**						
No vs. Yes	6.525	3.775-11.280	**< 0.001**	4.639	2.203-9.768	**< 0.001**
MGMT promoter methylation (Continuous)	0.004	0.000-0.070	**< 0.001**	0.134	0.010-1.815	0.131
HSPG2 expression (Continuous)	1.233	1.035-1.468	**0.019**	0.931	0.738-1.174	0.544
Oligoastrocytoma						
Age						
≥ 42 vs. < 42	3.325	1.399-7.904	**0.007**	2.651	0.968-7.258	0.058
KPS						
≤ 80 vs. > 80	3.056	1.207-7.734	**0.018**	1.665	0.62-4.472	0.311
***IDH1* mutation**						
No vs. Yes	11.308	4.289-29.813	**< 0.001**	8.953	2.562-31.289	**0.001**
HSPG2 expression (Continuous)	1.699	1.238-2.330	**0.001**	1.644	1.116-2.423	**0.012**
Oligodendroglioma						
Age ≥ 42 vs. < 42	4.506	2.002-10.141	**< 0.001**	3.839	1.668-8.836	**0.002**
***IDH1* mutation**						
No vs. Yes	2.257	1.13-4.508	**0.021**	0.986	0.39-2.498	0.977
***HSPG2* expression** (Continuous)	1.531	1.274-1.839	**< 0.001**	1.459	1.138-1.871	**0.003**

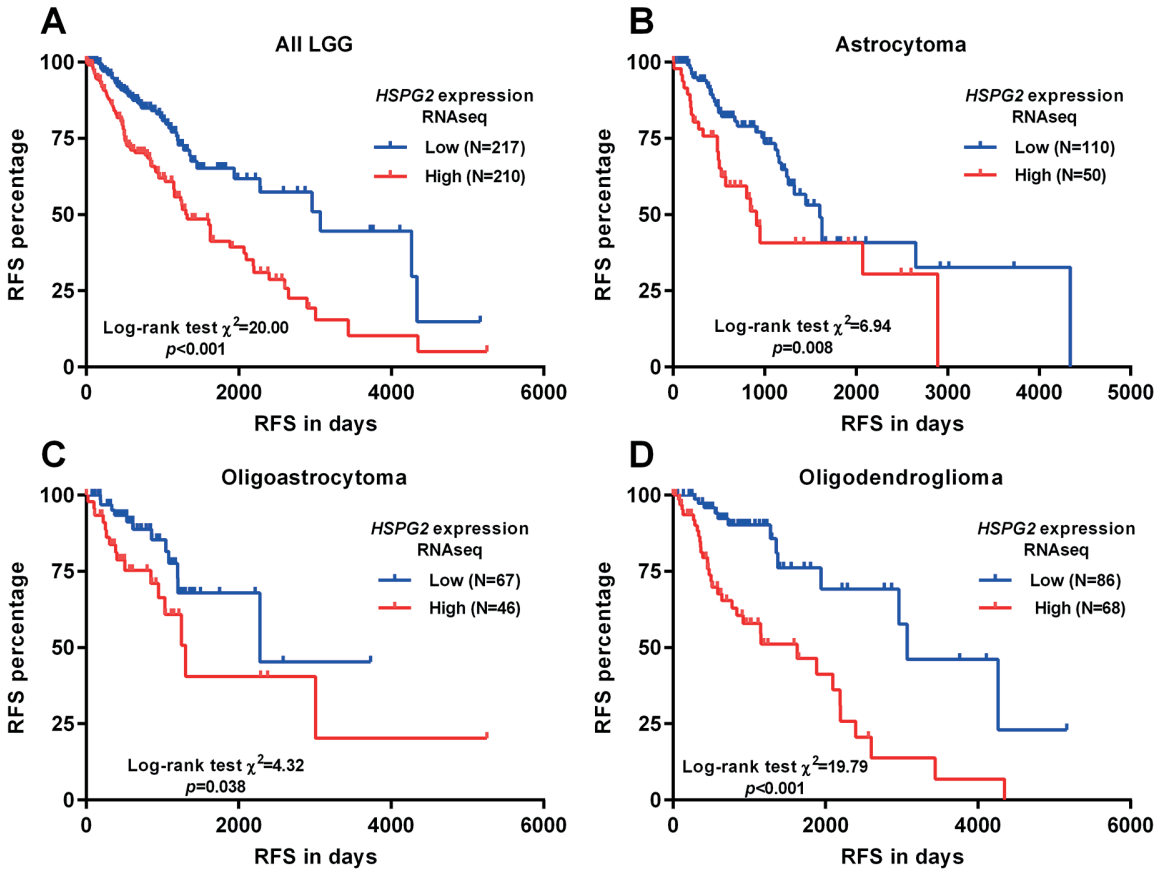

Figure 2. The association between HSPG2 expression and RFS in different subgroups of LGG. ***A-D.*** The Kaplan-Meier curves of RFS in LGG (A), astrocytoma ***(B)***, oligoastrocytoma ***(C)*** and oligodendroglioma ***(D)***. Patients were divided into two groups according to the best cutoff of HSPG2 expression. Data were from TCGA-LGG. Log-rank test was performed to assess the significance of the difference.

Table IV. Univariate and multivariate analyses of RFS in patients with primary LGG in TCGA-LGG.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***p***	**HR**	**95%CI**	***p***
Age						
≥ 42 vs. < 42	1.710	1.204-2.430	**0.003**	1.563	1.074-2.275	**0.020**
Gender						
Female vs. Male	1.241	0.875-1.752	0.219			
Subtypes						
Oligodendroglioma	1.000					
Astrocytoma	1.426	0.963-2.111	0.076			
Oligoastrocytoma	0.951	0.593-1.525	0.835			
KPS						
≤ 80 vs. > 80	2.185	1.461-3.267	**< 0.001**	1.776	1.170-2.696	**0.007**
***IDH1* mutation**						
No vs. Yes	3.292	2.249-4.817	**< 0.001**	2.091	1.313-3.328	**0.002**
MGMT promoter methylation						
(Continuous)	0.039	0.008-0.187	**< 0.001**	0.141	0.025-0.784	**0.025**
Targeted molecular therapy						
Yes vs. No	1.55	1.070-2.245	**0.020**	1.263	0.854-1.866	0.242
Radiation therapy						
Yes vs. No	1.431	0.973-2.106	0.069			
HSPG2 expression (Continuous)	2.223	1.556-3.206	**< 0.001**	1.030	0.899-1.181	0.671

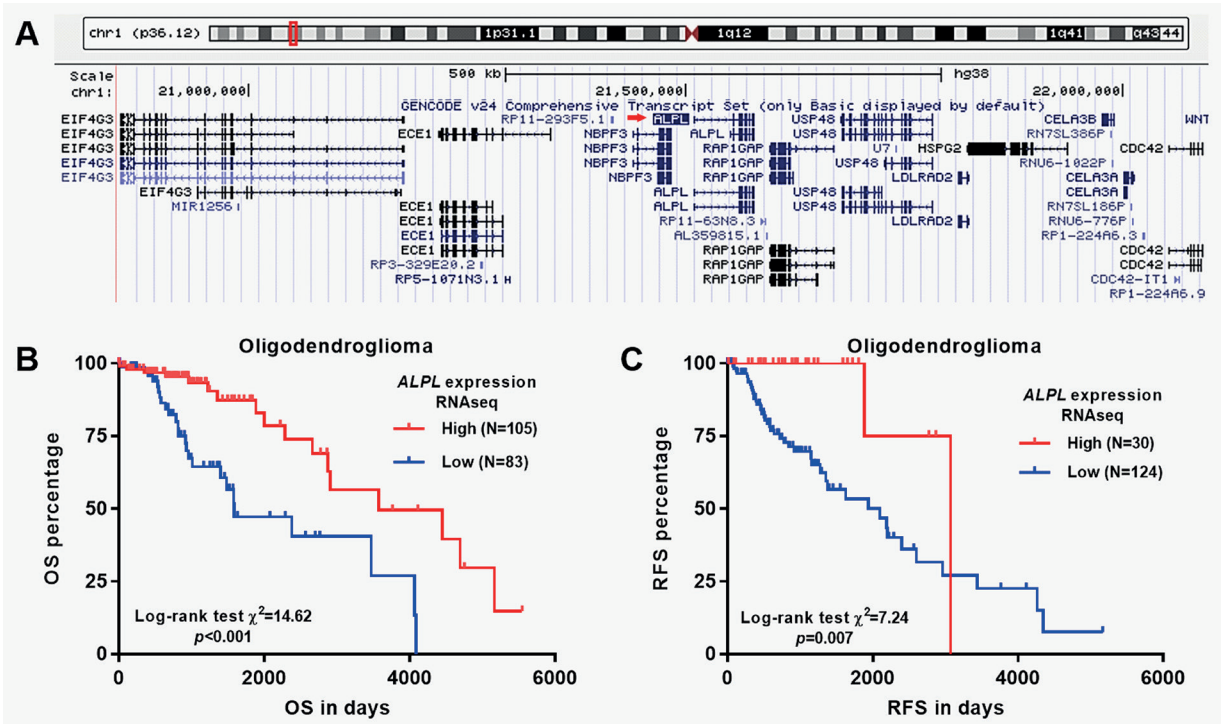

Figure 3. The association between ALPL expression and OS/RFS in oligodendroglioma. ***A,*** The genomic location of ALPL (red arrow) relative to HSPG2 in the human genome. ***B-C***, The Kaplan-Meier curves of OS (B) and RFS ***(C)*** in patients with oligodendroglioma. Patients were divided into two groups according to the best cutoff of ALPL expression. Data were from TCGA-LGG. Log-rank test was performed to assess the significance of the difference.

Table V. Univariate and multivariate analyses of RFS in patients with different subtypes of LGG in TCGA-LGG.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***p***	**HR**	**95%CI**	***p***
Astrocytoma						
Age						
≥ 42 vs. < 42	2.523	1.479-4.303	**0.001**			
KPS						
≤ 80 vs. > 80	3.283	1.797-5.998	**< 0.001**			
***IDH1* mutation**						
No vs. Yes	4.861	2.743-8.615	**< 0.001**			
MGMT promoter methylation						
(Continuous)	0.007	0-0.122	< 0.001			
***HSPG2* expression** (Continuous)	1.119	0.92-1.36	0.262			
Oligoastrocytoma						
***IDH1* mutation**						
No vs. Yes	3.118	1.233-7.885	**0.016**			
***HSPG2* expression** (Continuous)	1.196	0.853-1.678	0.299			
Oligodendroglioma						
IDH1 mutation						
No vs. Yes	2.176	1.105-4.285	**0.025**	1.295	0.582-2.882	0.526
HSPG2 expression (Continuous)	1.458	1.193-1.783	**< 0.001**	1.402	1.110-1.770	**0.005**

green frame). Therefore, we suggested that there might be other mechanisms underlying its dysregulation. By generating a comparable heatmap of HSPG2 expression and HSPG2 DNA methylation, we observed that HSPG2 RNA expression might be negatively associated with

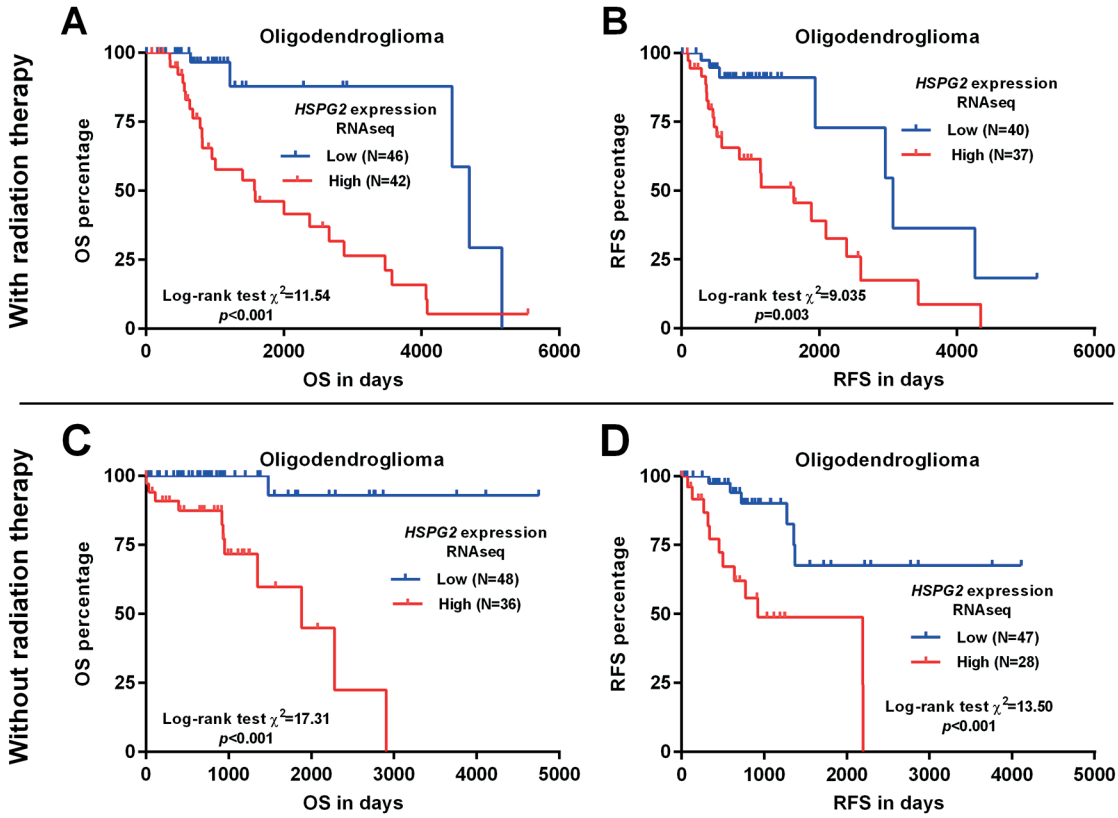

Figure 4. The association between HSPG2 expression and OS/RFS in oligodendroglioma with or without radiation therapy. ***A-D***. The Kaplan-Meier curves of OS (A and C) and RFS (B and D) in oligodendroglioma with (A-B) or without ***(C-D)*** radiation therapy. Patients were divided into two groups according to the best cutoff of HSPG2 expression. Data were from TCGA-LGG. Log-rank test was performed to assess the significance of the difference.

the methylation of some CpG sites (Figure 5C). Following regression analysis confirmed a weak negative correlation between HSPG2 expression and HSPG2 DNA methylation (Pearson's r = -0.388) (Figure 5D).

Discussion

Chromosomes 1p and 19q are frequently deleted in oligodendroglioma. The combined loss of 1p/19q has power independent prognostic value in LGG, which indicates improved responsiveness to procarbazine, lomustine, vincristine (PCV) and temozolomide chemotherapy and better overall survivals in oligodendroglioma[17]. Whole genome sequence analysis found that some regions in these two arm, such as 1p36/19q13 have many genes playing critical roles in tumorigenesis and oligodendrocyte differentiation[18], including WNT factors (WNT4, DVL1, and GSK3A), Notch-related factors (HES2-5, MINDBOMB2, and DLL3), apoptosis-related factors (BAX, CASPASE9, DFFA and DFFB), proto-oncogenes/oncogenes/tumor suppressors (p73, CHD5, SKI, HKR1, AKT2, TGFB1, ARHGAP35, and FOSB), and cancer related factors (mTOR, CEACAM1, PLAUR, RELB, and DYRK1B)[18]. Some genes harbored in these regions have specific prognostic power in gliomas. For example, downregulation of CHD5 is associated with a poor prognosis in human glioma[19]. Loss of 1p centromeric marker D1S2696 within NOTCH2 intron 12 was related to favorable prognosis in oligodendroglioma[20]. Epithelial membrane protein 3 (EMP3), which maps to 19q13.3 in the human genome, its promoter hypermethylation could predict favorable prognosis in patients with oligodendroglial tumors[21]. IDH-mutant glioma patients generally have low IGFBP2 expression, which is associated with improved survival independent of IDH status. In comparison, high IGFBP2 expression

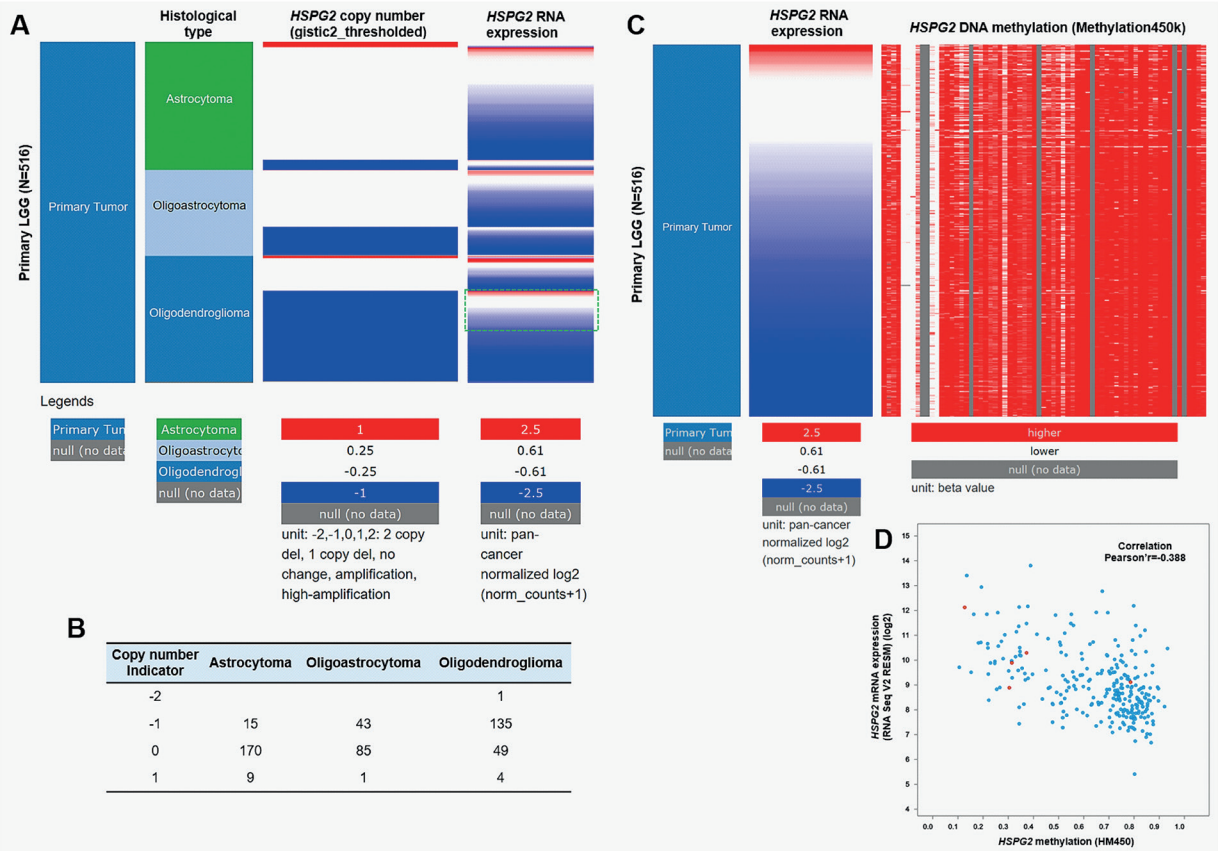

Figure 5. HSPG2 expression is modulated by DNA copy number and DNA methylation in oligodendroglioma. ***A,*** Heatmap of HSPG2 DNA copy number and HSPG2 RNA expression in astrocytoma, oligoastrocytoma and oligodendroglioma. ***B,*** The number of cases with 2 copy deletion (-2), 1 copy deletion (-1), no change (0), amplification (1) and high-amplification (2) in astrocytoma, oligoastrocytoma and oligodendroglioma. ***C,*** Heatmap of HSPG2 RNA expression and HSPG2 DNA methylation in all LGG. D. Regression analysis of the correlation between HSPG2 RNA expression and HSPG2 DNA methylation. Data were from TCGA-LGG.

is associated with worse survival in the IDH-wild type group[22]. In this work, by using the survival data the TCGA-LGG, we found that increased HSPG2 expression was an independent predictor of poor OS in oligoastrocytoma and oligodendroglioma. Besides, aberrant HSPG2 expression also independently predicted poor RFS in oligodendroglioma. However, by exploring the prognostic value of ALPL, which locates upstream of HSPG2 in 1p36, we found that ALPL expression might be a favorable marker in oligodendroglioma. Therefore, we infer that although 1p/19q co-deletion is a favorable prognostic marker in oligodendroglioma, the specific genes in these regions may have different prognostic value. In current clinical practice, for patients with WHO grade II/III gliomas, a combination of radiotherapy and chemotherapy is the preferred treatment after postsurgical treatment[17]. However, due to the potential adverse effects of surgery and long-term neurologic side effects of radiotherapy, a wait-and-see policy has been recommended in LGG patients who have had an extensive resection and in those who have expected favorable prognosis[23]. Although 1p/19q co-deletion is a powerful marker for prolonged RFS and OS in response to DNA-damaging treatments in general, it loses the prognostic power in patients with oligodendroglioma who receive no further radiotherapy or chemotherapy after surgery[7,24]. Therefore, it is quite meaningful to explore biomarkers that can predict prognosis in the patients without radiotherapy after surgery[25]. In this report, we further explored the association between of HSPG2 expression and survival outcomes in oligodendroglioma patients with or without radiotherapy. Our data confirmed that high HSPG2 expression was associated with significantly shorter OS and RFS, no matter the patients received radiotherapy or not.

To understand the mechanisms of dysregulated HSPG2 expression, we examined the correlation between HSPG2 expression and its DNA copy numbers. Although 1p/19q loss was common in oligodendroglioma, in 189 cases of oligodendroglioma with CNAs data, we found that 53 cases did not have copy number loss. HSPG2 RNA heatmap indicated that this proportion of patients had significantly higher HSPG2 expression compared with other patients. Epigenetic modification, such as methylation is also an important mechanism of dysregulated genes in glioma[26,27]. In this study, we also observed that HSPG2 RNA expression had a weak and negative correlation with its DNA methylation (Pearson's r = -0.388). Based on these findings, we infer that HSPG2 expression is modulated by both DNA copy number and DNA methylation in oligodendroglioma.

Conclusions

We observed that increased HSPG2 expression could independently predict poor OS in oligoastrocytoma and oligodendroglioma and also independently predicted poor RFS in oligodendroglioma. Its expression is modulated by both DNA copy number and DNA methylation in oligodendroglioma.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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