Panoramic RNA expression of fibroblast growth factors in human glioblastoma tissues and the impact on the survival of patients

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Abstract. Fibroblast growth factors (FGFs) have a key role in various critical steps of tumor growth and progression through effects on angiogenesis, inflammation and the growth and invasion of malignant cells. Nevertheless, the role of the FGF family in human glioblastoma (GBM) has been rarely studied. The objective of the present study was to assess the RNA expression of all FGF family members in tissues obtained from patients with GBM and to analyze the association between FGF expression and the survival of these patients. For this, the RNA expression of FGF family members in the malignant and proximal tissues of 12 patients with GBM was determined by analyzing high-throughput RNA transcriptome sequencing data uploaded to the National Center for Biotechnology Information database. The relationship between FGF genes and the survival of patients with GBM and glioma was also respectively studied by analyzing data from The Cancer Genome Atlas database using the Gene Expression Profiling Interactive Analysis tool. The results showed that the expression of FGF1, FGF17, FGF20 and FGF22 in GBM tissues was lower than that in adjacent tissues, with a difference of >2 times. Analysis of the overall survival of patients with GBM indicated there were no significant relationships between the expression of FGF1, FGF17, FGF20, FGF22 and overall survival. Analysis of the overall survival of patients with glioma showed that glioma patients with low FGF1 expression achieved a longer survival time than patients with high FGF1 expression; however, high expression of FGF17 and FGF22 indicated a longer survival time. In summary, the results of the present study demonstrated the panoramic expression of FGF family members in patients with GBM, and indicated that FGF1, FGF17 and FGF22 did not affect the survival of patients with GBM, but had a notable influence on the survival of patients with glioma.

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Introduction

Human gliomas are the most common and malignant primary tumors of the central nervous system (CNS). Despite the development of surgery, chemotherapy and radiation therapy, the median survival time of patients with this disease remains poor (1). Glioblastoma (GBM), the most lethal form of glioma, has a median overall survival time of only 15 months, which has remained unchanged over several years (2). In addition to the rapid proliferation, extensive invasion, tumor genetic heterogeneity and treatment resistance of GBM, the poor prognosis of patients also results from an insufficient understanding of the molecular pathogenesis and the lack of markers for timely diagnosis and sensitive treatments (2,3). Therefore, there is an urgent need to explore the reliable biomarkers of GBM progression to improve the treatment of this malignancy.

Fibroblast growth factors (FGFs) are broad-spectrum mitogens that regulate a number of cellular functions, including migration, proliferation, differentiation and survival (4). FGFs have been studied since the 1960s with regards to their function in fibroblast driven growth (5), and were formally purified and characterized nearly a decade after first identification (6). In mammals, FGFs exert their pleiotropic functions through binding and activating high-affinity tyrosine kinase receptors such as the fibroblast growth factor receptor (FGFR), which is encoded by four genes (FGFR1, FGFR2, FGFR3 and FGFR4) and FGFRL (a truncated FGFR without an intracellular domain) (4). The FGF/FGFR signaling system regulates a number of biological processes, such as embryogenesis, wound repair, tissue homeostasis and angiogenesis (7). Dysfunction of FGF/FGFR signaling has been observed in a variety of human diseases, such as chronic kidney disease, congenital craniosynostosis, dwarfism syndromes, obesity, insulin resistance and cancer. A number of studies have demonstrated that activation of the FGF/FGFR signaling system plays a key role in a variety of critical steps in tumor growth and progression through its effects on tumor and stromal cells, affecting angiogenesis, inflammation and tumor growth (8,9).

FGFs are highly associated with the development and progression of various human malignancies, including urothelial cancer, multiple myeloma, prostate cancer and hepatocellular carcinoma (4). Considering the importance of FGF signaling, it has attracted considerable interest in the study of multiple malignancies, where it plays a role in the proliferation, survival, self-renewal and invasion of tumor

cells (10). However, the role of FGF family members in GBM has been rarely explored, and most studies examining the role of FGFs were conducted *in vitro*. It has been reported that FGF2 is a oncogenic factor in glioma (11) and contributes to proliferation (12), the vascularization of glioma cells (13,14) and cancer stem cell self-renewal (15). FGF9 has been shown to potentially regulate the proliferation of human glioma cells either in the presence or absence of endogenous growth factor expression (16). Continued efforts to understand the correlation of FGFs with human GBM tissues will play a significant role in driving the discovery of novel diagnostic approaches and new therapies.

In the present study, the RNA expression of FGF members in human GBM tissues was first investigated by analyzing high-throughput RNA transcriptome sequencing data, then the effect of different FGF members on the overall survival of patients was further clarified. The present study therefore aimed to provide potential targets for diagnosis methods and the treatment of this malignancy.

Materials and methods

Human GBM and adjacent non-cancerous brain tissues (ANCBTs). Eligible patients with newly diagnosed and histologically confirmed GBM [World Health Organization (WHO) grade IV astrocytoma] (17), and who had undergone maximal safe surgery were included in the present study. Patients with GBM who had undergone radiotherapy, chemotherapy, immunotherapy and other new therapies were excluded from the present study. Human cancerous tissues and ANCBTs were collected from 12 patients with GBM admitted to the Department of Neurosurgery at The First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between December, 2016 and November, 2017, with written patient consent. Molecular and immunohistochemical biomarkers used for the diagnosis of these 12 patients with GBM included isocitrate dehydrogenase 1, glial fibrillary acidic protein, vimentin, p53, Ki-67 and O-6-methylguanine-DNA methyltransferase, information of which was obtained from the medical records from The Department Pathology at The First Affiliated Hospital of Sun Yat-sen University. Written patient consent was also obtained for the release of potentially personally-identifying clinical information. The present study was approved by the Institutional Ethics Review Board of The First Affiliated Hospital of Sun Yat-sen University [approval no. (2016)279] and complied with all relevant ethical regulations regarding human participants.

Analyzing high-throughput RNA transcriptome sequencing data. Previously, our team conducted high-throughput RNA transcriptome sequencing on tumors and adjacent tissues of the aforementioned 12 patients with GBM. The high-throughput RNA transcriptome sequencing was conducted and the procedure was clearly described in our previous study (18). The raw high-throughput RNA sequencing data was uploaded to the National Center for Biotechnology Information database with the (accession no. PRJNA525736). In the present study, the expression of FGF family members in GBM and proximal tissues was analyzed using this sequencing data. Data were mapped to the reference genome using the software TopHat2

(v.2.1.1), and then transcript abundance was quantified using RSEM (v.1.2.19).

Overall survival analysis. To further investigate the relationship between the expression of FGF family members and the overall survival of patients with GBM and glioma respectively, the 'Survival Analysis' tool (version 1.0) on Gene Expression Profiling Interactive Analysis (GEPIA; http://gepia.cancer-pku.cn/index.html) was used. The GBM and glioma datasets were respectively selected, and FGF1, FGF17, FGF20 and FGF22 (distinguishing high and low expression according to the median expression) were selected as the genes of interest. GEPIA datasets were originally from TCGA database. GEPIA used the log-rank test (sometimes termed the Mantel-Cox test) for the hypothesis evaluation, and P<0.05 was considered to indicate a statistically significant difference. The Cox proportional hazard ratio and the 95% confidence interval information were also included in the survival plot (19).

Statistical analysis. The data were analyzed using paired Student's t-test or χ^2 test. Statistical analysis was performed using GraphPad Prism 8.0 (Dotmatics) and SPSS (version 25.0; IBM Corp.) statistical software. P<0.05 was considered to indicate a statistically significant difference.

Results

FGF1, FGF17, FGF20 and FGF22 were differentially expressed in human GBMs and ANCBTs at the RNA level. Human cancerous GBM tissues and ANCBTs were collected from 12 patients. The median age of these patients was 45.5 years (range, 29-59 years), and there were 7 (58.3%) male and 5 (41.7%) female patients. All patients were diagnosed with GBM (WHO grade IV astrocytoma) and underwent maximal surgical resection. The clinicopathological characteristics of the patients with GBM are shown in Table I.

A panoramic visualization analysis was performed on the RNA expression of all members of the FGF family in human GBM tissues and ANCBTs (Table II). The result showed that the expression levels of four members, FGF1, FGF17, FGF20 and FGF22, were significantly lower in GBM tissues compared with the adjacent tissues, with a difference of >2 times (P<0.05; Fig. 1 and Table II). However, the expression of other FGF members in human GBM tissues and ANCBTs did not achieve both a difference of >2 times and statistical significance (Fig. 2 and Table II). To the best of our knowledge, these finding are the first to show the whole expression level of FGF family members in human GBM tissues and ANCBTs.

FGF1, FGF17 and FGF22 expression had a notable influence on the survival of patients with glioma. The impact of the expression of the aforementioned four FGF genes (FGF1, FGF17, FGF20 and FGF22) on the survival of patients with GBM and glioma was respectively analyzed using data from The Cancer Genome Atlas (TCGA) database. In TCGA dataset, the high FGF groups represented patients with ≥50% FGF expression compared with all patients, and the low FGF groups represented patients with <50% FGF expression compared with all patients. The expression levels of FGF1 (P=0.24), FGF17 (P=0.82), FGF20 (P=0.49) and FGF20

Table I. Clinicopathological characteristics of the patients with glioblastoma included in the present study.

Patient no.	Age, years	Sex	Stage	Therapy	IDH-1	GFAP	Vimentin	p53	Ki-67, %	MGMT
1	59	Male	IV	Resection	-	+	+	+	+, 20	+
2	56	Female	IV	Resection	-	+	+	+	+, 40	-
3	29	Male	IV	Resection	-	+	+	+	+, 60	+
4	36	Female	IV	Resection	-	+	+	+	+, 60	+
5	54	Male	IV	Resection	-	+	+	+	+, 50	+
6	45	Male	IV	Resection	-	+	+	+	+, 30	+
7	44	Male	IV	Resection	-	+	+	+	+, 60	+
8	59	Female	IV	Resection	-	+	+	+	+, 20	-
9	52	Male	IV	Resection	-	+	+	-	+, 80	+
10	46	Male	IV	Resection	-	+	+	+	+, 70	+
11	29	Female	IV	Resection	-	+	+	+	+, 50	+
12	37	Female	IV	Resection	-	+	+	+	+, 30	-

GFAP, glial fibrillary acidic protein; IDH-1, isocitrate dehydrogenase 1; MGMT, O-6-methylguanine-DNA methyltransferase.

Table II. Expression of the FGF family members in the high-throughput RNA sequencing data obtained from 12 pairs of human GBM tissues and ANCBTs.

ID	Symbol	GBM, average FPKM	ANCBT, average FPKM	GBM/ANCBT, fold change	P-value
ENSG00000113578	FGF1	49.8383	115.1533	2.3105	0.0003
ENSG00000078579	FGF20	0.3350	0.9567	2.8557	0.0019
ENSG00000070388	FGF22	0.1392	0.4067	2.9222	0.0047
ENSG00000158815	FGF17	1.0692	2.1883	2.0468	0.0137
ENSG00000161958	FGF11	17.4600	10.5225	0.6027	0.0082
ENSG00000156427	FGF18	0.0758	0.1425	1.8791	0.0302
ENSG00000129682	FGF13	5.2875	10.1283	1.9155	0.0462
ENSG00000070193	FGF10	0.1500	0.2917	1.9444	0.0567
ENSG00000118972	FGF23	0.0033	0.0000	0.0000	0.1039
ENSG00000140285	FGF7	0.4150	0.5500	1.3253	0.1260
ENSG00000138675	FGF5	0.2475	0.4342	1.7542	0.1942
ENSG00000111241	FGF6	0.0000	0.0108	0.0108/0	0.1990
ENSG00000075388	FGF4	0.0000	0.0008	0.0008/0	0.3388
ENSG00000186895	FGF3	0.0133	0.0000	0.0000	0.3388
ENSG00000196468	FGF16	0.0208	0.0358	1.7200	0.4303
ENSG00000162344	FGF19	0.0025	0.0008	0.3333	0.4382
ENSG00000102678	FGF9	1.2600	1.4583	1.1574	0.6505
ENSG00000102466	FGF14	10.3017	9.4483	0.9172	0.7533
ENSG00000114279	FGF12	25.5267	27.5492	1.0792	0.7617
ENSG00000138685	FGF2	10.8842	10.6917	0.9823	0.8232
ENSG00000105550	FGF21	0.0067	0.0075	1.1250	0.9089
ENSG00000107831	FGF8	0.1017	0.1017	1.0000	1.0000

ANCBT, adjacent non-cancerous brain tissue; FGF, fibroblast growth factor; FPKM, fragments per kilobase of transcript per million mapped reads.

(P=0.87) were not significantly correlated with the overall survival of the patients with GBM (Fig. 3). The relationship between these aforementioned FGFs and the overall survival of patients with glioma was then investigated. It was found that patients with glioma with low FGF1 expression achieved a longer survival time than patients with high FGF1 expression. Conversely, high expression of FGF17 and FGF22 indicated a longer survival time. In particular, the expression of FGF17
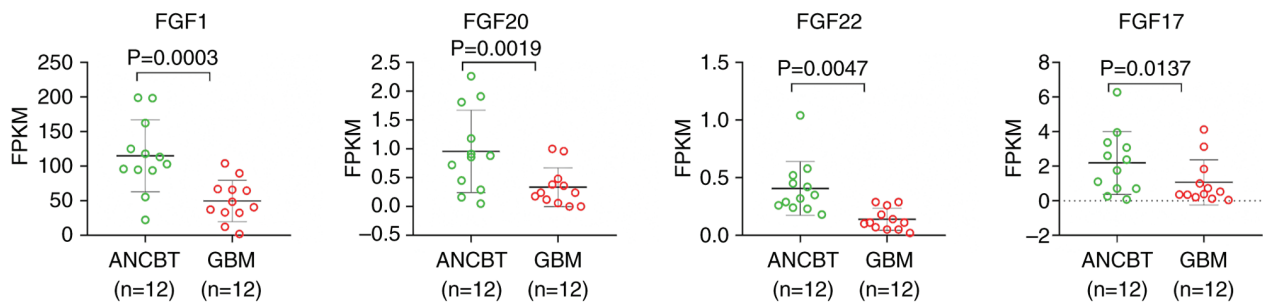
Figure 1. Expression of FGF family members in human GBM tissues and ANCBTs, in which a difference of >2 times with statistical significance (P<0.05) was observed. ANCBTs, adjacent non-cancerous brain tissues; FGF, fibroblast growth factor; FPKM, fragments per kilobase of transcript per million mapped reads; GBM, glioblastoma.

was most closely related to the survival of patients with glioma (P<0.001) (Fig. 4).

Discussion

The FGF family contains 22 members, which are typically divided into seven subfamilies based on evolutionary relationships, sequence similarity and biochemical functions, including the FGF1 (FGF1 and FGF2), FGF4 (FGF4, FGF5 and FGF6), FGF7 (FGF3, FGF7, FGF10 and FGF22), FGF8 (FGF8, FGF17 and FGF18), FGF9 (FGF9, FGF16 and FGF20), FGF19 (FGF19, FGF21 and FGF23) and FGF11 (FGF11, FGF12, FGF13 and FGF14) subfamilies (4,20). The results of the present study showed that the FGF1, FGF20, FGF22 and FGF17 expression levels were lower in GBM tissues compared with adjacent tissues, with a >2 times difference.

Among the FGF family members, FGF2 is one of the best characterized FGFs present in the CNS, and plays an important role in astrocyte proliferation, migration and maturation (21-23). FGF2 also promotes glioma cell growth, vascularization and cancer stem cell self-renewal (10). Experimental studies using FGF2-specific antisense oligonu-cleotides or antibodies to block glioma cell proliferation (24) and angiogenesis (25) have highlighted the relevance of the therapeutic targeting of FGF2 to increase survival time in glioma animal models. However, the expression of FGF2 in patients with GBM has not been focused upon. In the present study, a significant difference in FGF2 expression was not observed between tumor and adjacent tissues in patients with GBM. The expression of FGF2 was not correlated with the overall survival of patients with GBM.

FGF1 (also termed acidic FGF) is an autocrine/paracrine hormone that has historically been considered as a mitogen and has also attracted attention as an antidiabetic agent (26,27). In addition, FGF1 also promotes the repair process of damaged vessels (28). Thus, FGF1 could promote proliferation and resistance to chemotherapy in human pancreatic cancer cell lines (29). The characteristic ability of FGF1 promoting tumor cell proliferation and chemotherapy resistance may explain the finding that glioma patients with low FGF1 expression had longer overall survival times than patients with high FGF1 expression. However, the specific impact of FGF1 on glioma cells still needs further study. High expression of FGF1 has been found in non-small cell lung, ovarian, breast and prostate malignancies (30-32). The results of the present

study showed that FGF1 expression was 2 times lower in GBM tissues compared with adjacent tissues, which was inconsistent with a previous result indicating that FGF1 was upregulated in human glioma tissues and cell lines (33). Thus, further studies are needed to compare the expression levels of FGF1 in human GBM tissues and ANCBTs. The present study found that GBM patients with high FGF1 expression (n=81) did not achieve a significantly different survival time compared with GBM patients with low FGF1 expression (n=81). However, glioma patients with low FGF1 expression (n=338) had longer overall survival times compared with glioma patients with high FGF1 expression (n=338). The paradox with regard to the different actions of FGF1 expression on GBM and glioma maybe due to the relatively small number of patients with GBM that were included.

FGF17, a member of the FGF8/17/18 subfamily, contains an N-terminal cleaved signal peptide and can activate IIIc splice variants of FGFR 1-3 and FGFR4 (20). FGF17 is commonly expressed in the brain, endometrium, adrenal glands, thyroid and spleen (34). A recent study showed that FGF17 can induce the proliferation of oligodendrocyte progenitor cells in the brain, thereby improving memory in mice (35). It has also been shown that FGF17 is highly expressed in prostate cancer and aberrantly expressed in acute leukemia (34,36). However, to the best of our knowledge, there have been no reports considering the effect of FGF17 expression on overall survival in GBM. In the present study, the results of the RNA sequencing analysis showed that FGF17 expression was >2 times higher in adjacent tissues compared with tumor tissues in patients with GBM. In addition, the results of TCGA data analysis demonstrated that glioma patients with high FGF17 expression (n=337) achieved a longer survival time compared with glioma patients with low FGF17 expression (n=337). However, GBM patients with high FGF17 expression (n=81) did not achieve a significantly different survival time compared with GBM patients with low FGF17 expression (n=80). This is maybe due to small number of patients with GBM that were included, and further studies including greater numbers may change the association between the expression of FGF17 and the overall survival of patients with GBM.

FGF20 is a paracrine growth factor, the orthologs of which are highly conserved among vertebrates (37). FGF20 is predominantly expressed in the brain (38) and has being suggested to be a vital factor involved in brain development and neuronal homeostasis (39). FGF20 could enhance the
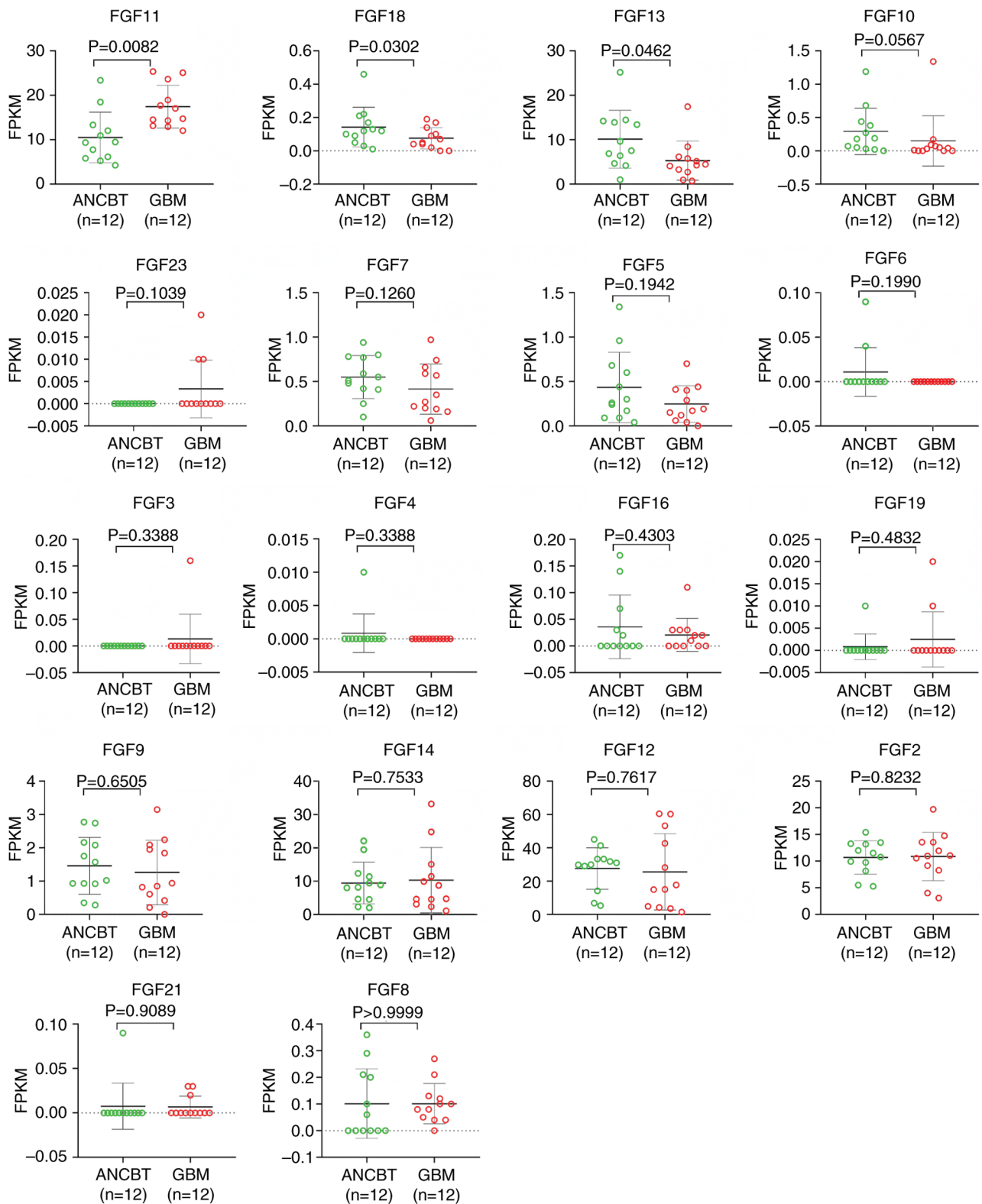
Figure 2. Expression of FGF family members in human GBM tissues and ANCBTs, in which a difference of <2 times was observed. The plots are arranged based on the P-value. ANCBTs, adjacent non-cancerous brain tissues; FGF, fibroblast growth factor; FPKM, fragments per kilobase of transcript per million mapped reads; GBM, glioblastoma.

survival of dopaminergic neurons in Parkinson's disease, and this means that FGF20 may have a neuroprotective function in the brain (40). A previous study found that FGF20 expression was upregulated in glioma cells following treatment with glucocorticoids (GCs), while a reduction in FGF20

expression in glioma cells significantly blocked the effect of GCs on macrophage polarization (41). However, to the best of our knowledge, there has been no research examining FGF20 expression in patients with GBM and it remains to be determined whether FGF20 expression is associated with the
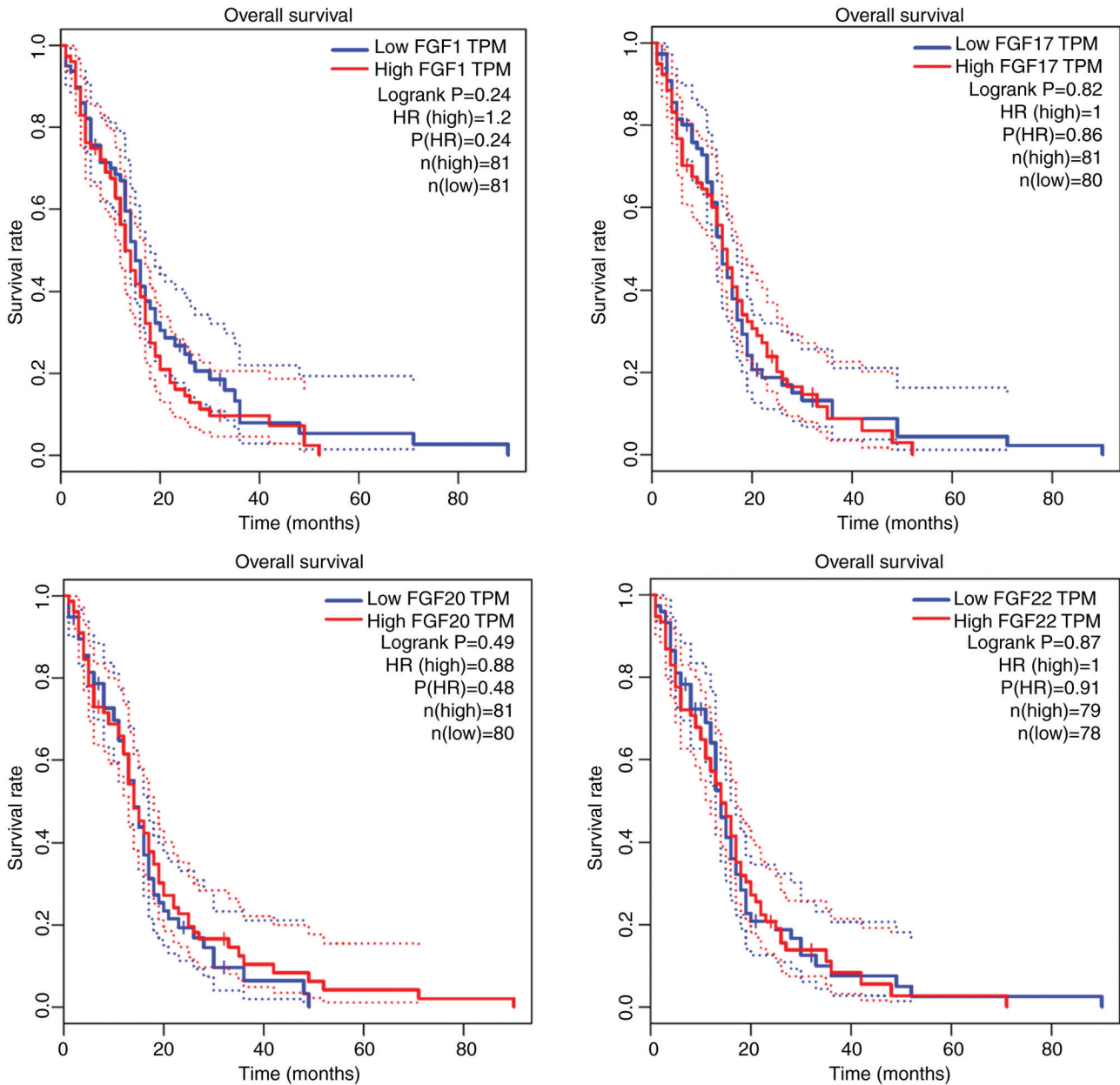
Figure 3. Overall survival of patients with glioblastoma with different expression levels of FGF1, FGF17, FGF20 and FGF22. FGF, fibroblast growth factor; HR, hazard ratio; TPM, transcripts per million.

prognosis of these patients. In the present study, the results showed that FGF20 expression in human GBM tissues was nearly 3-fold lower than that in ANCBTs. However, the results from TCGA database analysis did not identify a relationship between the FGF20 expression level and the overall survival of patients with GBM and glioma, respectively.

FGF22, a target-derived presynaptic organizer critical in the formation of novel excitatory synapses during development and the organization of synapses in adult brains (42,43), has become a crucial endogenous contributor of detour circuit formation (44). Previous studies have shown that FGF22 plays a critical role as a presynaptic organizer in the formation of new synapses in adult remodeling spinal cords (45) and that delivery of FGF22 may promote organization of the presynapse, promoting the plasticity of healthy supraspinal axons and thereby contributing to the recovery of function in incomplete

spinal cord injury (44). However, there have been no studies examining the relationship between FGF22 and GBM and whether FGF22 expression affects the survival of patients with GBM. In the present study it was shown that the FGF22 expression level in adjacent tissues was nearly three times higher than that in GBM tissues. In addition, following analysis of TCGA data, it was found that GBM patients with high FGF22 expression (n=79) did not achieve a significantly different survival time compared with GBM patients with low FGF22 expression (n=78). However, it was found that glioma patients with high FGF22 expression (n=337) had a longer survival time than glioma patients with low FGF22 expression (n=333).

In summary, in the present study, the RNA expression levels of FGF family members in human GBM tissues were first investigated by analyzing high-throughput RNA transcriptome sequencing data. It was found that the expression
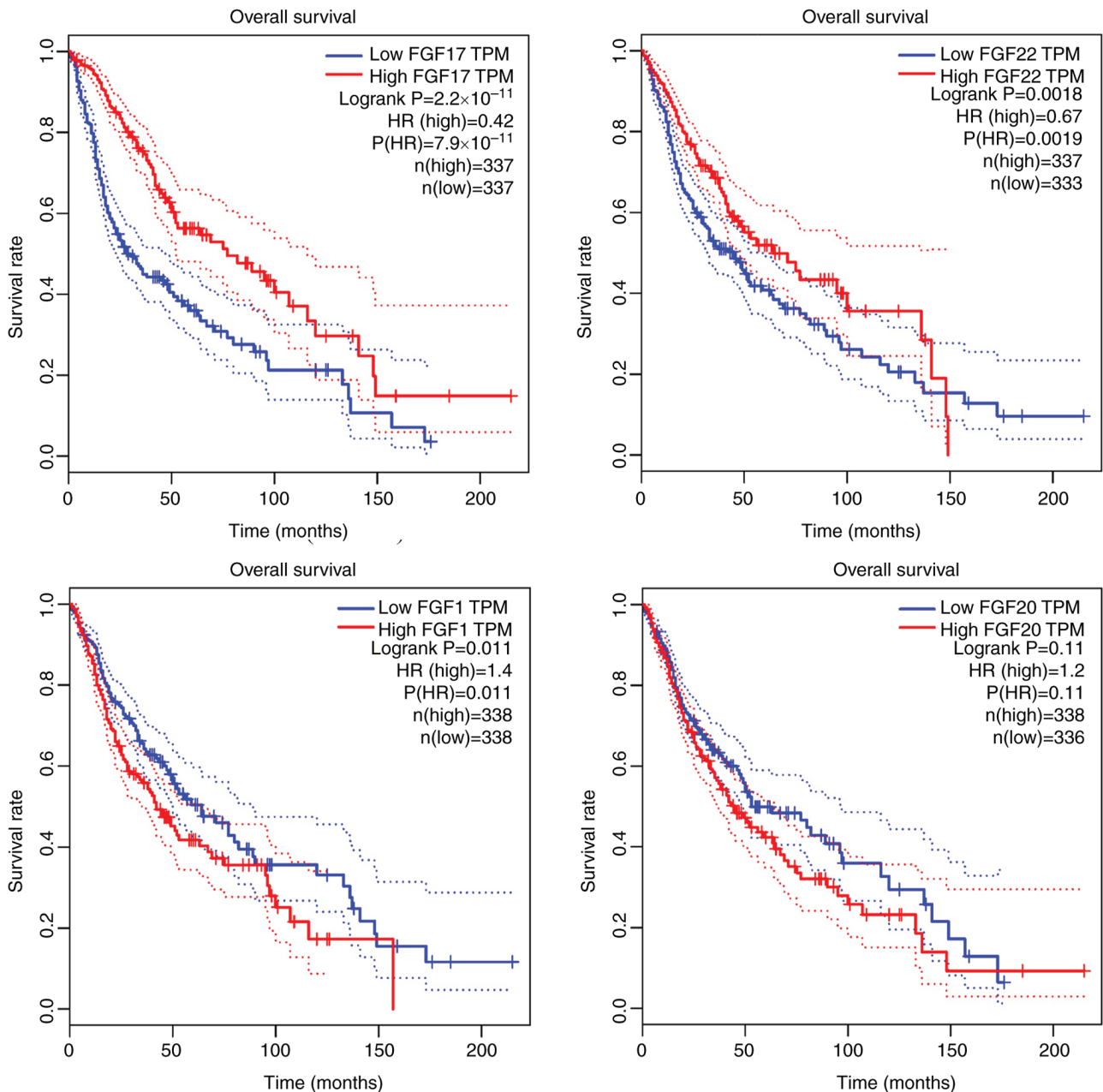
Figure 4. Overall survival of patients with glioma with different expression levels of FGF1, FGF17, FGF20 and FGF22. FGF, fibroblast growth factor; HR, hazard ratio; TPM, transcripts per million.

levels of four members, FGF1, FGF20, FGF22 and FGF17, were >2 times lower in GBM tissues compared with adjacent tissues. The different expression levels of FGF1, FGF17, FGF20 and FGF22 did not have a significant influence on the overall survival of the patients with GBM. However, it was identified that patients with glioma with low FGF1 expression achieved longer overall survival time than patients with high FGF1 expression. By contrast, high expression of FGF17 and FGF22 indicated a longer overall survival time. The expression level of FGF17 was most closely related to the longer overall survival time of patients with glioma. The present study is therefore expected to provide a certain research basis for clinical gene therapy of these malignancies.

However, there are some limitations to the present study. The present study mainly focused on the RNA levels of FGFs in patients with GBM through analyzing RNA transcriptome sequencing data, and the FGF protein levels were therefore not detected in the present study. The protein levels of FGFs in human GBM will be examined in a further study. In addition, further research is still needed to explore whether and how FGF1, FGF17, FGF20 and FGF22 affect the proliferation or invasion abilities of human GBM. Moreover, the overall survival curves were obtained through the GEPIA analysis tool, which generates survival curves based on data from TCGA database. In addition, since whole datasets could not be obtained from all research within TCGA and as FGF expression was only tested in 12 patients in The First Affiliated Hospital of Sun Yat-sen University, survival outcomes in this study could only be obtained via the GEPIA analysis tool, which may have led to a bias in the overall survival data analysis.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Author's contributions

KZ designed the study, analyzed the sequencing data and wrote the manuscript. JX and BZ made contributions to the analysis and interpretation of data. KZ and JX confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Human GBM tissues and adjacent non-cancerous brain tissues were collected from the Neurosurgery Department of the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) with written patient consent. The present study was approved by The Institutional Ethics Review Board of the First Affiliated Hospital of Sun Yat-sen University [approval no. (2016)279] and complied with all relevant ethical regulations regarding human participants.

Patient consent for publication

Written patient consent was obtained for the publication of potentially personally-identifying clinical information.

Competing interests

The authors declare that they have no competing interests.

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