Fam20C Overexpression Predicts Poor Outcomes and is a Diagnostic Biomarker in Lower-Grade Glioma

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Glioma is a relatively low aggressive brain tumor. Although the median survival time of patients for lower-grade glioma (LGG) was longer than that of patients for glioblastoma, the overall survival was still short. Therefore, it is urgent to find out more effective molecular prognostic markers. The role of the Fam20 kinase family in different tumors was an emerging research field. However, the biological function of Fam20C and its prognostic value in brain tumors have rarely been reported. This study aimed to evaluate the value of Fam20C as a potential prognostic marker for LGG. A total of 761 LGG samples (our cohort, TCGA and CGGA) were included to investigate the expression and role of Fam20C in LGG. We found that Fam20C was drastically overexpressed in LGG and was positively associated with its clinical progression. Kaplan-Meier analysis and a Cox regression model were employed to evaluate its prognostic value, and Fam20C was found as an independent risk factor in LGG patients. Gene set enrichment analysis also revealed the potential signaling pathways associated with Fam20C gene expression in LGG; these pathways were mainly enriched in extracellular matrix receptor interactions, cell adhesion, cell apoptosis, NOTCH signaling, cell cycle, etc. In summary, our findings provide insights for understanding the potential role of Fam20C and its application as a new prognostic biomarker for LGG.

Keywords: FAM20C, lower-grade gliomas, LGG, biomarker, prognosis, bioinformatics

INTRODUCTION

Malignant central nervous system tumors account for 31.5% of nervous system tumors, and gliomas account for 80.7% of malignant central nervous system tumors (Goodenberger and Jenkins 2012; Ostrom et al., 2018). Global cancer statistics in 2018 showed that nervous system cancer was the 19th most common cancer in the world, with 296,851 new cases, accounting for 1.6% of the total cancer incidence, and 241,037 deaths each year, accounting for 2.5% of the total case mortality (Bray et al., 2018). According to the World Health Organization (WHO) 2016 version of the central nervous
系统分类，胶质瘤包括WHO II级和III级星形细胞瘤，II级和III级少突胶质细胞瘤，以及IV级胶质母细胞瘤（Louis et al., 2016; Wasseling and Capper 2018）。

目前，低级胶质瘤的标准治疗包括手术切除，辅以术后放疗和化疗（Stupp et al., 2005）。然而，肿瘤的预后仍差。胶质母细胞瘤（GBM）是成人最恶性的脑肿瘤类型。尽管在改善目前治疗方法后，中位生存期仅为17～23个月（Xu et al., 2017; Jiang et al., 2019）。WHO II级和III级胶质瘤的中位生存期长于WHO IV级胶质母细胞瘤，中位生存时间为1.7–13.3年（Buckner et al., 2016; Mair et al., 2021; van den Bent 2014）。这种差异广泛存在于低级别的胶质瘤患者中。有些患者可以在没有接受任何治疗的情况下存活很多年；然而，其他患者可能在治疗后迅速恶化。由此可见，寻找更多有效的分子标志物对于治疗低级别胶质瘤至关重要。由于低级别胶质瘤的异质性，理解其发生机制和生物学背景对于发现有效的治疗标志物具有重要意义。

Fam20基因家族是一个新发现的分泌性激酶家族。该家族成员包括Fam20A、Fam20B和Fam20C（Nalbant et al., 2005; Zhang et al., 2018）。Fam20C是Fam20家族中一种重要激酶，它在Golgi体中磷酸化了一系列的分泌蛋白质（Tagliabracci et al., 2014; Cozza et al., 2018）。蛋白质磷酸化修饰是指通过将磷酸基团从ATP或GTP转移至氨基酸残基的过程来磷酸化蛋白质。这一过程调节了细胞中许多蛋白质的磷酸化，包括代谢性调节、转录调节、细胞周期、骨架重排、凋亡和分化（Manning et al., 2002; Sreelatha et al., 2015）。异常的蛋白质磷酸化是许多疾病，包括癌症的首要原因。Fam20C在低级别胶质瘤中的表达与肿瘤细胞凋亡和细胞周期密切相关。更重要的是，许多Fam20C的底物与肿瘤细胞凋亡和增殖相关。其中包括胰岛素样生长因子结合蛋白7（IGFBP7），它依赖于Fam20C磷酸化，可诱导细胞迁移（Bieche et al., 2004; Georges et al., 2011）。然而，Fam20C作为潜在的肿瘤诊断和预后标志物尚未被充分开发。

在本研究中，我们发现Fam20C在多种癌症中过表达，包括LGG。高表达的Fam20C与肿瘤进展相关。因此，Fam20C可以作为诊断和预后标志物。此外，转录表达Fam20C在LGG患者中可能是一个独立的风险因素。因此，Fam20C的磷酸化和肿瘤发生相关，进而影响细胞外基质受体、细胞粘附和细胞周期。我们的结果证实了Fam20C在诊断和预后标志物中具有重要价值。

**MATERIALS AND METHODS**

**Data Acquisition and Processing**

LGG基因表达数据和临床信息数据来自《癌症基因组图谱数据库》（http://cancergenome.nih.gov/）和《中国胶质瘤基因图谱数据库》（http://www.cgga.org.cn）。从TCGA数据集，我们获得了529个LGG样本的原始miRNA-seq数据，其中使用了用于R包的原始数据（版本4.0.2）。从CGGA数据库，我们获得了529个LGG样本的原始RNA-seq数据，其中使用了用于R包的原始数据（版本4.0.2）。从CGGA数据库，我们获得了原始RNA-seq数据的529个LGG样本的原始RNA-seq数据，其中使用了用于R包的原始数据（版本4.0.2）。此外，我们使用了来自《癌症基因组图谱数据库》和《中国胶质瘤基因图谱数据库》的原始RNA-seq数据。

**Patient Information and Ethics**

这项研究由900th Hospital of Joint Logistics Support Force于2016年和2020年11月进行，所有患者均接受了脑肿瘤手术。根据WHO 2007和2016年标准，所有患者均被临床诊断为II级和III级胶质瘤。患者年龄小于16岁且在诊断时存活的患者被排除。每个样本的RNA-seq数据由Sanger sequencing进行测序，以获得每个样本的原始数据。

**Immunohistochemistry Analysis**

一项包含LGG和正常大脑区域的实验，从900th Hospital of Joint Logistics Support Force收集了正常大脑区域的数据。这些正常大脑区域的样本被固定在40 g/L的甲醛溶液中，常规包埋于石蜡中。从CGGA数据库，我们获得了100个LGG患者的原始RNA-seq数据，其中包括正常大脑区域的3个样本。这些正常大脑区域的样本被固定在40 g/L的甲醛溶液中，常规包埋于石蜡中。从CGGA数据库，我们获得了100个LGG患者的原始RNA-seq数据，其中包括正常大脑区域的3个样本。这些正常大脑区域的样本被固定在40 g/L的甲醛溶液中，常规包埋于石蜡中。
The expression of FAM20C in different types of cancer was obtained from the CCLE database, including glioma (n = 66), chondrosarcoma (n = 4), mesothelioma (n = 11), meningioma (n = 3), kidney (n = 37), upper aerodigestive (n = 33), thyroid (n = 12), giant cell tumour (n = 3), melanoma (n = 63), soft tissue (n = 20), neuroblastoma (n = 17), breast (n = 60), osteosarcoma (n = 10), liver (n = 29), esophagus (n = 27), Ewing’s sarcoma (n = 12), medulloblastoma (n = 4), bile duct (n = 8), lung NSC (n = 136), pancreas (n = 46), ovary (n = 55), urinary tract (n = 28), endometrium (n = 28), prostate (n = 8), lung small cell (n = 54), stomach (n = 39), acute myeloid leukemia (n = 39), leukemia other (n = 5), lymphoma Hodgkin (n = 13), colorectal (n = 63), B cell acute lymphoblastic leukemia (n = 13), T cell acute lymphoblastic leukemia (n = 16), chronic myelogenous leukemia (n = 15), lymphoma DLBCL (n = 18), multiple myeloma (n = 29), B cell lymphoma other (n = 16), T cell lymphoma other (n = 11), and lymphoma Burkitt (n = 11). The expression of FAM20C in different types of cancer was obtained from Tumor Immune Estimation Resource database, including ACC (n = 77), BLCA (n = 423), BRCA (n = 1197), CESC (n = 309), CHOL (n = 45), COAD (n = 516), DLBC (n = 47), ESCA (n = 199), GBM (n = 163), HNSC (n = 563), KICH (n = 91), KIRC (n = 595), KIRP (n = 318), LAML (n = 173), brain LGG (n = 518), LIHC (n = 419), LUAD (n = 542), LUSC (n = 542), MESO (n = 87), OV (n = 428), PAAD (n = 183), PCPG (n = 188), PRAD (n = 544), READ (n = 102), SARC (n = 264), SKCM (n = 462), STAD (n = 444), TGCT (n = 137), THCA (n = 571), THYM (n = 120), UCEC (n = 187), UGS (n = 57), and UVM (n = 79). *p < 0.05; **p < 0.01; ***p < 0.001.

Gene Set Enrichment Analysis (GSEA)

GSEA was conducted to detect whether a set of a priori defined genes showed statistically significant differential expression between the high and low Fam20C expression groups during the MSigDB set enrichment process, with 1000 genome

4 μm-thick sections, and stained with HE. The EliVision method was used for Fam20C immunohistochemical staining and the results were observed through light microscopy. Anti-Fam20C polyclonal antibody, was purchased from Abcam, UK (product number ab154740). Non-biotin universal two-step immunohistochemistry kit (mouse/rabbit enhanced polymer detection system) was purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. The positive control tissue in this experiment was glioblastoma tumor tissues (Du et al., 2020). Results interpretation criteria: Fam20C positive expression means brown-yellow particles in the nucleus and cytoplasm. Dark brown in the nucleus and cytoplasm of the cells was defined as a strong cell; Cells with yellow or brown nucleus and cytoplasm were defined as medium-strength cells; The nucleus and cytoplasm of the cells were light yellow or had faintly visible staining, which was defined as a weak intensity cell. No staining of nucleus and cytoplasm was negative. The histochemical score (H-score) was employed to quantify the expression of Fam20C. H-score = (percentage of weak intensity cells×1) + (percentage of medium intensity cells 2) + (percentage of strong cells×3).
permutations performed per analysis. In this study, GSEA first generated an ordered list of all genes based on the correlation between the genes and Fam20C expression. Then, GSEA was performed to clarify the significance of the difference in survival between the high and low Fam20C expression groups. The expression level of Fam20C was used as the phenotype label. The phenotypic enrichment pathways were ranked by the |p| values and normalized enrichment score. The calculation results were given using the ggplot2 R packages.

Functional Enrichment Analysis
Gene Ontology (GO) was employed to detect the function of the differentially expressed genes. The analysis gained a new understanding of the biological effects of Fam20C. The genes related to Fam20C expression (absolute Pearson correlation coefficient > 0.5 and p < 0.05) were regarded as risk score-related genes, and their potential biological functions and pathways were determined. The Ggplot2 software package in R software was employed to analyze the GO pathways. The enrichment analysis of GO was based on a p-value and a q-value threshold < 0.05.

Statistical Analysis
The Wilcoxon signed-rank test was used to detect the expression of Fam20C. The correlation between the clinicopathological characteristics and Fam20C expression was tested with the Wilcoxon signed-rank test. The survival ROC software package in R software was used to generate receiver operating characteristic (ROC) curves to evaluate the diagnostic value of Fam20C expression. The area under the curve represents the diagnostic value. Using the Survival package in R, the overall survival (OS) rates of the high expression group and the low expression group were compared by Kaplan-Meier analysis. Univariate Cox analysis was used to determine the potential survival rate, and multivariate Cox analysis was used to determine whether Fam20C expression was an independent risk factor for OS in LGG patients. p < 0.05 was considered statistically significant. All data were processed using R software (version 4.0.2) and Adobe Photoshop CC.

RESULTS
Fam20C Was Overexpressed in LGG
Data from the Cancer Cell Line Encyclopedia (CCLE) database showed that Fam20C was highly expressed in multiple cancer cell lines, especially glioma (Figure 1A). At present, there are few studies on the relationship between Fam20C and tumorigenesis. To determine the expression of Fam20C in other tumors, we conducted a comprehensive analysis of 33 tumors in TCGA. Among them, there were five cancer types in which Fam20C was overexpressed (Figure 1B).

Overexpressed Fam20C Was Associated With Advanced LGG
Next, we analyzed the correlation between the level of Fam20C mRNA in LGG patients and their clinicopathological parameters. The TCGA database includes the patient’s tumor grade, sex, and survival status. The CGGA database includes the patient’s tumor grade, sex, survival status, IDH mutation/wild-type, and 1p19q joint deletion status. As shown in Figure 2A, the higher the grade of the tumor, the higher the Fam20C expression level. In addition, in the TCGA database, high expression of the Fam20C gene was positively related to grade and survival status but not to sex. In the CGGA database, higher Fam20C expression was related to grade, survival status, IDH wild-type, and 1p19q nonjoint deletion but not to sex (Figure 2A and Supplementary Figure S1).

Since high expression of Fam20C in LGG patients was related to tumor grade, we further tried to determine whether this overexpression of Fam20C in LGG patients was related to a poor prognosis through the use of Kaplan-Meier curves. As shown in Figure 2B, higher Fam20C expression levels were significantly correlated with a worse OS in both the TCGA and CGGA datasets (Figure 2B). In general, the results showed that the expression of Fam20C was significantly associated with poorer OS in both databases.
High Fam20C Expression Served as an Independent Risk Factor Among LGG Patients

Univariate and multivariate Cox analyses were utilized to evaluate the independent prognostic values of Fam20C expression in LGG patients. The univariate analysis results showed that high Fam20C expression was significantly correlated with a shorter OS (HR = 1.02, 95% CI: 1.01–1.03, p < 0.001; HR = 1.01, 95% CI: 1.00–1.01, p = 0.001) in TCGA and CGGA. Other variables related to poor survival included age and grade in TCGA (Supplementary Table S2). In CGGA, variables related to poor survival that including grade IDH and 1p19q (Supplementary Table S3). Multivariate analysis showed that high expression of Fam20C in LGG patients was independently associated with a significant decrease in OS (Figure 3 and Supplementary Tables S2, S3).

Fam20C Expression Is a Novel Diagnostic Biomarker for LGG

To evaluate the diagnostic value of Fam20C for LGG, TCGA RNA-seq data were employed to draw the ROC curve. The area

FIGURE 3 | Multivariate Cox analysis evaluating independently predictive ability of Fam20c for OS in TCGA and CGGA database. **p < 0.01; ***p < 0.001.
under the ROC curve was 0.690, which had high diagnostic value (Figure 4A). This result was further verified with the CGGA data set, and the area under the ROC curve was 0.778 (Figure 4B).

**Functional Enrichment Analysis**

To clarify the functions and signaling pathways of genes co-expressed with Fam20C, we performed GO and KEGG enrichment analyses. GO analysis results showed that co-expressed genes were mainly closely related to the biological process of extracellular matrix remodeling (Figure 5A). KEGG analysis showed that co-expressed genes were mainly enriched in extracellular matrix receptor interactions, cell adhesion, apoptosis, cancer pathways, P53 signaling pathways, NOTCH signaling pathways, and cell cycle signaling pathways (Figure 5B).

**Fam20C Was Also Overexpressed in Our Cohort**

To further verify the expression of Fam20C in our cohort, we detected its expression in our clinical samples and found that Fam20C was significantly overexpressed in grade 3 tumors (Figure 6A). Higher Fam20C expression levels were also correlated with a worse OS in our cohort (Figure 6B).

Univariate and multivariate Cox analyses were utilized to evaluate the independent prognostic values of Fam20C expression in LGG patients. The univariate analysis results showed that high Fam20C expression was significantly correlated with a shorter OS (HR = 6.39, 95% CI: 1.86–21.86, p = 0.003). Other variables related to poor survival included IDH 1p19q and extent of resection (Supplementary Table S4). Multivariate analysis showed that high expression of Fam20C in LGG patients was independently associated with a significant decrease in OS (Figure 6C and Supplementary Table S4).

**DISCUSSION**

Glioma is one of the most common primary malignant tumors in the nervous system. It arises from active glial cells in the brain, including astrocytes, oligodendrocytes, and ependymal cells.
Although the prognosis of lower-grade glioma is better than that of glioblastoma, there are still some lower-grade gliomas with a poor prognosis and a short survival time, and 70% of low-grade patients undergo a high-grade transformation within 10 years. Therefore, early diagnosis and accurate prognostic biomarkers are essential for improving the prognosis of patients with LGG.

In recent years, a class of secreted kinases has been newly discovered that are involved in the regulation of many important physiological reactions. The Fam20 kinase family includes Fam20A, Fam20B, and Fam20C (Nalbant et al., 2005; Zhang et al., 2018). Fam20C is a casein kinase enriched in the Golgi apparatus that modulates many downstream substrates through protein phosphorylation and plays an important role in the formation of the secretome of tumor cells. However, its diagnostic and prognostic value in cancer is still unclear. Our results provide insights for further understanding the pathological role of Fam20C in promoting tumor growth and invasion and its potential value as a diagnostic and prognostic marker for LGG.

Fam20C protein kinase has a significant promotion effect on the metastasis and invasion of triple-negative breast cancer (Tagliabracci et al., 2015). Fam20 is also a potential target gene related to the pathogenesis of early lung adenocarcinoma (Kang et al., 2013). Therefore, we speculate that the expression of Fam20C may affect the survival of patients through promoting the progression of tumor cells. However, the expression of Fam20C in cancer and its effects on other important aspects, such as tumor cell metastasis, still lack consensus. It has been previously reported that insulin-like growth factor binding protein 7 (IGFBP-7) regulates the migration of glioma cells through the AKT-ERK pathway, thereby playing an important role in the growth and migration of gliomas (Jiang et al., 2008). Adult diffuse glial tumor GWAS contains variants of D2HGDH and Fam20C in different molecular subtypes. In IDH mutant gliomas, the nine variants located on chromosome two of D2HGDH and those in its vicinity are all significant genome-wide (Eckel-Passow et al., 2020).

In this study, we systematically detected the expression level of Fam20C in different types of cancer in the TCGA database. Based on the available evidence, our results indicated that Fam20C expression was elevated in breast cancer. In addition, Fam20C was also overexpressed in five other cancers, such as glioma, meningioma, and kidney cancer, and Fam20C overexpression was associated with higher-grade gliomas.

FIGURE 6 | Expressions, immunohistochemistry and multivariate Cox analysis of Fam20C in our cohort. (A) Representative figures of Fam20C immune-staining in our clinical LGG samples (20X; grade II: n = 60, grade III: n = 40, normal: n = 3); (B) Kaplan–Meier curve evaluating the correlation between Fam20C protein expression and LGG patients’ survival (FAM20C low vs high, low n = 51, high n = 49, p < 0.001; Log rank test); (C) Multivariate Cox analysis evaluating independently predictive ability of Fam20C for OS.
In this study, we investigated whether Fam20C could be used as a diagnostic and therapeutic target for GBM (Du et al., 2020). However, there have been few studies on the Fam20C gene in LGG. Hence, we further investigated whether Fam20C could be used as a diagnostic and prognostic marker for LGG. Our present data has demonstrated that Fam20c may be a potential prognostic and diagnostic signature for LGG patients based on two databases (TCGA and CGGA) and clinical samples. This biomarker could efficiently stratify the LGG patients into two groups with distinct survival differences. Moreover, we identified the potential signaling pathways of Fam20C in LGG patients. Overexpression of Fam20C was correlated with progressive malignancy and poor survival of LGG patients and was associated with significant enrichment of extracellular matrix receptor interactions, cell adhesion and apoptosis in LGG. Taken together, our results suggest that Fam20C inhibition could be a potential therapeutic target to prevent LGG progression.

CONCLUSION

In conclusion, we established a potential prognostic and diagnostic signature for LGG patients based on two databases (TCGA and CGGA) and clinical samples. This biomarker could efficiently stratify the LGG patients into two groups with distinct survival differences. Moreover, we identified the potential signaling pathways of Fam20C in LGG patients. Overexpression of Fam20C was correlated with progressive malignancy and poor survival of LGG patients and was associated with significant enrichment of extracellular matrix receptor interactions, cell adhesion and apoptosis in LGG. Taken together, our results suggest that Fam20C inhibition could be a potential therapeutic target to prevent LGG progression.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories at: http://github.com/fengjing0314/jing. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF performed conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of article. JZ and LZ performed provision of study materials or patients, collection and assembly of data, data analysis and interpretation, article writing, and final approval of manuscript. BX, FX, and XQ performed provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. DM performed provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. GC performed conception and design, administrative support, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. XW performed collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. HZ and JW performed conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, article writing, and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2021.757014/full#supplementary-material
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