The Expression and Prognostic Values of Epidermal Growth Factor Receptor Family in Glioma

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Abstract

Background: Epidermal growth factor receptor (EGFR) family belongs to the transmembrane protein receptor of tyrosine kinase I subfamily, including 4 members, they are EGFR/ERBB1, ERBB2, ERBB3, ERBB4. The EGFR family is closely related to the occurrence and development of a variety of cancers.

Material/Methods: In this research, we used multiple online bioinformatics websites including ONCOMINE, TCGA, CGGA, TIMER, cBioPortal, GeneMANIA and DAVID to study the expression profiles, prognostic values and immune infiltration correlations of EGFR family in glioma.

Results: We found that EGFR and ERBB2 mRNA expression levels were the higher in glioblastoma (GBM, WHO IV) than other grades (WHO grade II&III), While ERBB3 and ERBB4 mRNA expression levels were opposite. EGFR and ERBB2 were notably downregulated in IDH mutant gliomas, while ERBB3 and ERBB4 were the opposite. Besides, ERBB2 and ERBB4 in glioma patients were associated with poor prognosis. In addition, correlation analysis between EGFR family expression and immune infiltrating levels in glioma showed that EGFR family expression and immune infiltrating levels were significantly correlated. PPI network of EGFR family in glioma and enrichment analysis showed that EGFR family and their interactors mainly participated in regulation of cell motility involved integrin receptors and Rho family GTPases.

Conclusions: In summary, this study indicates that EGFR family may become potential targets and new prognostic markers for glioma.

Background

Brain and central nervous system (CNS) cancers (collectively referred to as CNS cancers) are responsible for substantial morbidity and mortality worldwide between 1990 and 2016[1]. Glioma is a common brain tumor in human and one of the most malignant tumor among all cancers[2, 3]. Although various treatments for glioma including surgery, radiotherapy, systemic therapy, tumor treatment fields, and supportive treatment, have recently made progress, the median survival period is still maintained at about 15 months, and long-term survival is unsatisfactory[4]. Because current treatments cannot significantly improve patient outcomes, the discovery of novel treatment strategies is critical. Therefore, the identification of new biomarkers is of great significance for improving the prognosis and individualized treatment.

Epidermal growth factor receptor (EGFR) family (also known as HER family) belongs to the transmembrane protein receptor of tyrosine kinase I subfamily, including 4 members, they are EGFR/ERBB1、ERBB2、ERBB3、ERBB4,encoded by the proto-oncogene ERBB1-4. The members of the EGFR family are similar in structure and consist of an extracellular ligand-binding domain, a hydrophobic transmembrane region and an intracellular segment containing a conserved tyrosine kinase domain[5, 6]. After the ligand binds to the extracellular domain, the protein conformation of the extracellular domain is changed. Phosphorylation of the tyrosine kinase in the intracellular domain initiates the signal transduction pathway, transmits the signal from outside the cell to the cell, and regulates the cell's response to external stimuli, thereby regulating the growth, survival, transformation and apoptosis of normal cells[7, 8]. Overexpression and activation of the EGFR family can be seen in many human cancers, and is closely related to the clinicopathological characteristics and prognosis

of many tumors, such as breast cancer[9], lung cancer[10], gastric cancer[11] and melanoma[12]. Previous studies have discovered the results of EGFR family pathway dysregulation and its relationship with the clinical characteristics and prognosis of human gliomas. However, the expression and clinical prognosis of EGFR family in gliomas are still a tremendous problem that urgently needs attention.

In recent years, due to the continuous development and application of bioinformatics databases, more and more tumor biomarkers have been discovered[13–16]. At present, more and more studies have shown that EGFR family can be used as potential targets for the treatment of glioma[17, 18]. In this study, we downloaded EGFR family expression data from various online databases, and analyzed the relationship between their transcription levels in gliomas and clinical prognosis. The analysis of the tumor immune estimation resource (TIMER) database exhibited the correlation between the EGFR family and tumor infiltrating immune cells in the tumor microenvironment. Our research shows that the EGFR family may be a potential target with promising prognostic value in glioma patients.

Materials And Methods

Oncomine database analysis

We used the Oncomine database (https://www.oncomine.org/)[19] to extract the data of expression level of the EGFR family in various types of glioma tissues. Then, we analyzed the expression of EGFR family between cancer tissue and normal tissue through Student's t test. Critical value setting conditions: Fold change>1.5, P-value<0.01.

Acquisition of the data from the TCGA and CGGA dataset

The data of RNA-sequencing and clinical information in TCGA-GBMLGG dataset were downloaded from UCSC Xena (https://xenabrowser.net/datapages/)[20]. Besides, the data of RNA-sequencing and clinical information in CGGA dataset (mRNAseq_325) were also obtained from official website (http://www.cgga.org.cn/index.jsp)[21]. For further analysis, a total 668 samples from the TCGA dataset and 326 primary glioma samples from the CGGA dataset, which contained both gene expression and survival data were extracted.

Tumor infiltrating immune cells analysis

The TIMER database (https://cistrome.shinyapps.io/timer/) is a database that can comprehensively and systematically analyze the interaction between tumors and immunity[22]. We downloaded estimated data of Tumor infiltrating immune cells from TIMER database and analyzed the correlation between the expression levels of EGFR family and the abundance of immune infiltrating cells in glioma.

cBioPortal analysis

cBioPortal (https://www.cbioportal.org/) provides a visual tool for research and analysis of cancer gene data, and help cancer tissue and cytology research to gain molecular data understanding and understanding of genetics, epigenetics, gene expression and proteomics. We can study the link between genetic change and clinical practice by customizing the interface of the data. Through the cBioPortal online tool, we analyzed of EGFR family alterations and correlation. We used the dataset for glioma, which further analyzed EGFR family expression using cBioPortal[23].

GeneMANIA analysis

GeneMANIA database (http://www.genemania.org/) is a website dedicated to the study of protein-protein interaction (PPI) relationships[24]. It mainly provides data predictions including the following proteins: protein prediction, protein interaction, Co-expression, sharing of protein domains, subcellular co-localization, signaling pathways, genetic interactions, etc. construct a PPI network. In this study, human (homo sapiens) was selected in the species selection interface to search for interacting proteins of the EGFR family.

DAVID analysis

DAVID (https://david.ncifcrf.gov/) is a public database that integrates biological data and analysis tools, which can annotate genes and pathways[25]. GO is a bioinformatics tool that annotates genes and analyzes the biological processes in which they participate. KEGG is a database used to analyze the relevant signal pathways in the large-scale molecular data set generated by high-throughput experimental technology. Using DAVID was used for GO enrichment analysis of the EGFR family in three aspects: molecular function (MF), cell composition (CC) and biological process (BP), as well as the enrichment analysis of KEGG pathway, to clarify the gene function and the cell signaling pathways of the EGFR family.

Statistical Analysis

Use Student's t-test to analyze gene expression in Oncomine, TCGA and CCGA databases as well as IDH wild-type and mutation data in TCGA and CCGA databases. The survival curves were compared using the log-rank test. Correlation analysis is evaluated using Spearman's correlation analysis in the timer database. $P<0.05$ was considered statistically significant.

Results

The mRNA expression levels of EGFR family across different types of cancers

The Oncomine database was used to compare the mRNA levels of EGFR family between the tumor and normal tissues. This analysis revealed that the EGFR family expression was significant differences compared with the normal tissues in glioma (Figure. 1). According to the information from the datasets in Oncomine, in Sun’s datasets[26], the mRNA levels of EGFR was 9.390, 5.740, 8.211 times higher in glioma tissues with

different histological types than normal tissues, respectively (Table 1). In TCGA's dataset, the expression of EGFR was 3.792 and 2.956 times higher in glioma tissues with different histological types than normal tissues, respectively (Table 1). In French's dataset[27], the expression of EGFR was 9.847 times higher in Anaplastic Oligodendroglioma tissues than normal tissues (Table 1). In Lee's dataset[28], the expression of EGFR was 3.772 times higher in Glioblastoma tissues than normal tissues (Table 1). In Shai's dataset[29], the expression of EGFR was 3.815 times higher in Glioblastoma tissues than normal tissues (Table 1). In Bredel's dataset[30], the expression of EGFR was 5.840 times higher in Glioblastoma tissues than normal tissues (Table 1). In Murat's dataset[31], the expression of EGFR was 10.667 times higher in Glioblastoma tissues than normal tissues (Table 1). In Watson's dataset[32], the expression of ERBB2 was 5.166 times higher in Meningioma tissues than normal tissues (Table 1). In Bredel's dataset[33], the expression of ERBB2 was 3.065 times higher in Glioblastoma tissues than normal tissues (Table 1). In pomeroy's dataset[34], the expression of ERBB3 was 8.973 times higher in Classic Medulloblastoma tissues than normal tissues (Table 1). ERBB4 has no research results that meet the screening criteria.

Table 1
In different types of gliomas and normal brain tissues, differences in the transcriptional level of the EGFR family

EGFR family	Type of glioma vs. brain	Fold change	P	t-test	Reference
EGFR	Glioblastoma vs. Normal	9.390	3.09E-27	14.885	Sun[14]
	Oligodendroglioma vs. Normal	5.740	1.39E-15	10.540	Sun[14]
	Anaplastic Astrocytoma vs. Normal	8.211	9.39E-8	7.824	Sun[14]
	Brain Glioblastoma vs. Normal	3.792	5.10E-18	14.875	TCGA
	Anaplastic Oligodendroglioma vs. Normal	9.847	4.07E-9	9.400	French[15]
	Glioblastoma vs. Normal	3.772	9.78E-7	8.111	Lee[16]
	Glioblastoma vs. Normal	3.815	2.75E-5	4.729	Shai[17]
	Glioblastoma vs. Normal	5.840	9.51E-7	6.098	Bredel[18]
	Brain Glioblastoma vs. Normal	2.956	9.32E-101	26.116	TCGA
	Glioblastoma vs. Normal	10.667	1.16E-6	10.112	Murat[19]
ERBB2	Meningioma vs. Normal	5.166	8.89E-7	7.324	Watson[20]
	Glioblastoma vs. Normal	3.065	1.70E-9	10.222	Bredel[18]
ERBB3	Classic Medulloblastoma vs. Normal	8.973	3.79E-8	6.404	Pomeroy[21]
ERBB4	NA	NA	NA	NA	NA

Subtype analysis of mRNA expression levels of EGFR family in glioma

To analyze transcription levels of EGFR family in subtypes of glioma patients, TCGA and CGGA database was applied. According to tumor grades, In the TCGA database, compared with WHO II & III, the EGFR transcription level was the highest in WHO IV (Figure 2A). However, by analyzing the CGGA RNA-seq database, we were found that this difference was not statistically significant (Figure 2E). In the TCGA database, the transcription level of ERBB2 was the highest in WHO IV compared with WHO II&III (Figure 2B). While, the transcription levels of ERBB3 and ERBB4 in WHO IV were significantly lower than those of II&III, and were statistically significant (Figure 2C and D). Analysis of the CGGA RNA-seq data set also found that the transcription levels of ERBB2, ERBB3 and ERBB4 had similar expression levels (Figure 2F, G and H). In summary, the mRNA levels of EGFR and ERBB2 were higher in advanced and poorly differentiated gliomas, however, the mRNA levels of ERBB3 and ERBB4 were lower in advanced and poorly differentiated gliomas.

Mutations of isocitrate dehydrogenase (IDH) play an important role in the occurrence and development of glioma and serve as a potential prognostic marker for patients with glioma[35]. Therefore, we started to study the expression level of EGFR in IDH mutant and wild type. Studies have shown that in the TCGA data, the expression level of EGFR in IDH wild-type glioma is elevated (Figure. 3A), however, in the CGGA RNA-seq data set, there was no significant difference in the expression level of EGFR in IDH wild-type glioma (Figure. 3E). In the TCGA data, the expression level of ERBB2 in IDH wild-type gliomas was notably increased (Figure. 3B), as well as in CGGA RNA-seq datasets (Figure. 3F). Analysis of TCGA data and CGGA RNA-seq data set found that ERBB3 and ERBB4 increased notably in IDH mutant gliomas (Figure. 3C and D), as well as in CGGA RNA-seq datasets (Figure. 3G and H). In conclusion, data analysis shows that the expression level of the EGFR family is notably different in different IDH states, and has the potential to become a biomarker of IDH subtypes of glioma.

Correlation between EGFR family expression and immune infiltrating levels in glioma

More and more studies have shown that tumor-infiltrating lymphocytes can be used as related indicators to predict tumor metastasis and invasion[36, 37]. Therefore, by analyzing the TIMER database, we found the correlation between the expression level of the EGFR family and the level of immune infiltration in patients with glioma. As shown in Figure 4 and Table 2, the expression level of EGFR mRNA was notably positively correlated with the level of B cell infiltration in patients with glioma ($r=0.1671$, $p<0.0001$). The expression level of EGFR mRNA was notably negatively correlated with the infiltration level of DCs ($r=-0.09997$, $p=0.0088$) and CD4+T cells ($r=-0.1143$, $p=0.0027$) of glioma patients. ERBB2 mRNA expression was notably positively correlated with the level of macrophage infiltration in gliomas ($r=0.1026$, $p=0.0072$). The expression of ERBB3 and ERBB4 mRNA in gliomas was notably positively correlated with the level of CD4+T cells infiltration (ERBB3, $r=0.1200$, $p=0.0016$, ERBB4, $r=0.09663$, $p=0.0114$). The expression of ERBB3 and ERBB4 mRNA in gliomas was notably negatively correlated with the level of B cell infiltration (ERBB3, $r=-0.08882$, $p<0.0201$,

ERBB4, r=-0.1591, p<0.001). These results strongly suggest that the EGFR family plays a specific role in regulating the immune infiltration of glioma.

Table 2
Correlation between EGFR family mRNA expression level and immune cell infiltration level

Description	EGFR		ERBB2		ERBB3		ERBB4	
	Cor	P	Cor	P	Cor	P	Cor	P
B-cell	0.1671	<0.0001	0.02272	0.5527	-0.08882	0.0201	-0.1591	<0.0001
CD4-Tcell	-0.1143	0.0027	0.03041	0.4268	0.1200	0.0016	0.09663	0.0114
CD8-Tcell	0.05893	0.1233	0.07340	0.0549	-0.002242	0.9533	-0.01364	0.7217
Neutrophil	-0.04326	0.2582	0.06590	0.0848	-0.02445	0.5229	-0.06434	0.0925
Macrophage	0.07331	0.0551	0.1026	0.0072	-0.01798	0.6386	-0.05173	0.1763
Dendritic cell	-0.09997	0.0088	0.06210	0.1044	-0.01882	0.6229	-0.06135	0.1087

PPI network of EGFR family in glioma and enrichment analysis

Next, we used Gene-MANIA to construct a PPI network for EGFR family, and the result is shown in Figure 6A. Then, GO and KEGG analyses based on DAVID were performed to identify the functional enrichment of EGFR family and their associated genes (Table 3). Biological processes (BP) enrichment term exhibited that EGFR family and their cooperators were significantly associated with ERBB2 signaling pathway, regulation of cell motility, regulation of phosphatidylinositol 3-kinase signaling, phosphatidylinositol phosphorylation, phosphatidylinositol-mediated signaling, peptidyl-tyrosine phosphorylation, epidermal growth factor receptor signaling pathway, MAPK cascade, transmembrane receptor protein tyrosine kinase signaling pathway, positive regulation of GTPase activity, wound healing, and positive regulation of cell proliferation; MF enrichment showed that EGFR family were significantly correlated to phosphatidylinositol-4,5-bisphosphate 3-kinase activity, Ras guanyl-nucleotide exchange factor activity, epidermal growth factor receptor binding, ephrin receptor binding, and receptor signaling protein tyrosine kinase activity; KEGG enrichment revealed that EGFR family were related to ERBB signaling pathway, Glioma, Non-small cell lung cancer, Neurotrophin signaling pathway, Chronic myeloid leukemia, Ras signaling pathway, MicroRNAs in cancer, Proteoglycans in cancer, Focal adhesion, Prostate cancer, Pathways in cancer, Estrogen signaling pathway and Endometrial cancer. Overall, the potential mechanisms that EGFR family participate in the carcinogenesis of glioma were explored by PPI construction and enrichment analysis.

Table 3
GO and KEGG enrichment analysis of EGFR family and their 20 interactors.

Category	Terms	Description	Count	FDR
BP	GO:0038128	ERBB2 signaling pathway	12	2.95E-21
BP	GO:2000145	regulation of cell motility	10	2.63E-17
BP	GO:0014066	regulation of phosphatidylinositol 3-kinase signaling	10	6.11E-13
BP	GO:0046854	phosphatidylinositol phosphorylation	10	3.83E-12
BP	GO:0048015	phosphatidylinositol-mediated signaling	10	1.18E-11
BP	GO:0018108	peptidyl-tyrosine phosphorylation	10	3.45E-10
BP	GO:0007173	epidermal growth factor receptor signaling pathway	8	1.01E-09
BP	GO:0000165	MAPK cascade	10	4.45E-08
BP	GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	8	5.02E-08
BP	GO:0043547	positive regulation of GTPase activity	11	1.83E-06
BP	GO:0042060	wound healing	6	9.38E-05
BP	GO:0008284	positive regulation of cell proliferation	9	1.55E-04
MF	GO:0046934	phosphatidylinositol-4,5-bisphosphate 3-kinase activity	10	5.51E-14
MF	GO:0004713	protein tyrosine kinase activity	11	7.11E-13
MF	GO:0005088	Ras guanyl-nucleotide exchange factor activity	10	1.84E-11
MF	GO:0005154	epidermal growth factor receptor binding	6	5.20E-07
MF	GO:0046875	ephrin receptor binding	5	4.08E-05
MF	GO:0004716	receptor signaling protein tyrosine kinase activity	4	2.80E-04
KEGG	hsa04012	ERBB signaling pathway	18	2.00E-29
KEGG	hsa05214	Glioma	8	1.53E-07
KEGG	hsa05223	Non-small cell lung cancer	7	4.12E-06
KEGG	hsa04722	Neurotrophin signaling pathway	8	1.21E-05
KEGG	hsa05220	Chronic myeloid leukemia	7	1.93E-05
KEGG	hsa04014	Ras signaling pathway	9	4.27E-05
KEGG	hsa05206	MicroRNAs in cancer	9	2.66E-04
KEGG	hsa05205	Proteoglycans in cancer	8	4.15E-04
KEGG	hsa04510	Focal adhesion	8	5.07E-04

KEGG	hsa05215	Prostate cancer	6	0.002482
KEGG	hsa05200	Pathways in cancer	9	0.003013
KEGG	hsa04915	Estrogen signaling pathway	6	0.004453
KEGG	hsa05213	Endometrial cancer	5	0.00888

BP, Biological processes; MF, molecular functions; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, gene ontology; FDR, false discovery rates.

The relationship between EGFR family alterations and prognosis in patients with glioma

In order to further understand the EGFR family, we used the cBioPortal online tool to study the alterations of EGFR family and its correlation with prognosis. We found that among 885 patients with glioma, there were 272 patients with alterations of EGFR family genes (31%), and the most common mutation was amplification (Figure 5A). In addition, the cBioPortal database shows that EGFR family genetic alterations and overall survival (OS) ($p < 0.001$), disease free survival (DFS) ($p < 0.001$), disease-specific survival (DSS) ($p < 0.001$), Progression free survival (PFS) of patients with glioma and glioma ($p < 0.001$) (Figure 5B, C, D, and E). We used Pearson's test to study the correlation between the expression levels of the EGFR family in the CGGA and TCGA datasets. The results of the study demonstrated next EGFR family to be notably positively correlated: EGFR with ERBB2; ERBB3 with ERBB4; the following EGFR family to be significantly negatively correlated: EGFR with ERBB3; ERBB2 with ERBB3 and ERBB4. While the expression of EGFR had no association with ERBB4 (Figure 6B and C).

Prognostic values of EGFR family in glioma

In addition, we used the TCGA dataset and CGGA dataset to evaluate the prognostic impact of EGFR family expression on full-grade glioma. The results showed that high mRNA levels of ERBB2 and ERBB4 in glioma patients were associated with poor prognosis (Figure 7C, D, G and H), while the expression of EGFR and ERBB3 had no correlation with the prognosis of glioma patients (Figure 7A, B, E and F). Based on the CGGA and TCGA data sets, the results indicated that the prognosis of EGFR families in glioma patients is similar. Next, through univariate Cox analysis, we found that age, tumor grade, IDH mutation and EGFR family were the prognostic factors of glioma patients (Table 4).

Table 4
Univariate regression analysis was used to predict the overall survival rate of glioma patients.

Characteristic	TCGA (n=668)			CGGA (n=326)		
Univariate	P	HR	95%CI	P	HR	95%CI
Age	<0.0001	1.068	1.057-1.078	<0.0001	1.054	1.038-1.070
Gender	0.144	0.826	0.639-1.068	0.806	1.044	0.741-1.469
Grade	<0.0001	4.638	3.803-5.657	<0.0001	1.952	1.708-2.232
IDH status	<0.0001	0.127	0.096-0.169	<0.0001	2.802	1.960-4.007
EGFR	<0.0001	1.187	1.103-1.278	0.808	1.013	0.914-1.123
ERBB2	<0.0001	2.177	1.884-2.516	<0.0001	1.961	1.613-2.384
ERBB3	0.001	0.879	0.818-0.946	0.005	0.866	0.783-0.958
ERBB4	<0.0001	0.684	0.638-0.734	<0.0001	0.630	0.564-0.703

Discussion

Glioma is an invasive and highly diffuse brain tumor[38]. Current standard treatment for glioma patients includes maximum safe surgical resection, simultaneous radiotherapy and temozolomide, and then adjuvant temozolomide. Glioma is still an incurable disease, the average OS after standard treatment is 12–15 months, and relapse is inevitable[39]. Therefore, it is extremely important to explore new methods to improve the prognosis of glioma patients and improve the quality of life of patients. Research results in recent years have shown that the tumor microenvironment plays an important role in the occurrence and development of glioma. An in-depth understanding of the tumor microenvironment is beneficial to provide new immunotherapy for glioma patients to inhibit tumor development[40, 41]. In recent years, immune checkpoint inhibitors against members of the EGFR family of gliomas have been widely tested in clinical trials, opening up broad prospects for the treatment of gliomas[42, 43]. In this study, we analyzed the expression of EGFR family members in gliomas, the relationship with prognosis, and immune infiltration. It suggests that the EGFR family mRNA level is related to the poor prognosis of glioma. In addition, EGFR family mRNA levels are correlated with the abundance of tumor-infiltrating immune cells. Overall, our study provides new insights into the important role of the EGFR family in the assessment of glioma prognosis and immune infiltration.

The abnormal expression of the EGFR family in large number of human cancers has been studied, however the study of the EGFR family in gliomas is still uncertain[44, 45]. Here, in order to clarify the expression profile of the EGFR family in all grades of gliomas, by analyzing the glioma samples in the CGGA and TCGA data sets, we summarized the expression patterns and distribution of the EGFR family. We found that the expression of EGFR family in glioma has significant changes in mRNA levels. At the same time, the expression of EGFR family in various subtypes in gliomas is significantly different, suggesting that the expression of EGFR family is related to malignant phenotype and tumor progression. In addition, the EGFR

family is significantly different in IDH-mutated gliomas, suggesting that IDH may be a regulator of the EGFR family.

After binding and activation, EGFR can form a dimer structure with other members. It preferentially binds to ERBB2 to form a stronger heterodimer. It initiates a series of cascade reactions through autophosphorylation, participates in cell signal transmission, and converts signals. It spreads into the nucleus and plays an important role in normal cell proliferation, differentiation and migration[46]. EGFR gene amplification and overexpression can be seen in a variety of human malignancies, including non-small cell lung cancer[47], breast cancer[48], ovarian cancer[49], gastric cancer[50], and etc. Abnormal EGFR gene activation is closely related to tumor cell proliferation, angiogenesis, tumor invasion and migration, and inhibition of apoptosis[51].

ERBB2 forms a heterodimer with other members of the family, indirectly binds to the ligand, activates the tyrosine kinase in the intracellular segment, triggers downstream signal transduction, and the signal is transmitted to the nucleus through the intercellular substance, activating cell proliferation-related genes, thereby Promote cell mitosis, regulate cell proliferation, differentiation, migration and tumor formation[52, 53]. ERBB2 is overexpressed to varying degrees in various malignancies such as breast cancer[54], ovarian cancer[55], non-small cell lung cancer[56], gastric cancer[57], and *etc.*.

ERBB3 / ERBB2 dimer is the most active ERBB dimer in ERBB dimer, which can activate PI3K/AKT Jak/Stat and other signaling pathways, regulate cell proliferation, differentiation, migration and other activities[58]. ERBB3 is closely related to the occurrence and development of various tumors. Abnormal activation and overexpression of the HER3 gene can be seen in malignant tumors such as breast cancer[59], gastric cancer[60], ovarian cancer[61], prostate cancer[62], and *etc.*.

After binding ERBB4 with ligands (neurodifferentiation factor heparin binding epidermal growth factor, etc.), it activates downstream PI3K/Akt Ras/Raf/MAPK signaling pathways through autophosphorylation, and mediates extracellular growth factor signaling through the intracellular kinase cascade Intracellular transmission, thereby regulating angiogenesis and cell growth, differentiation, proliferation and apoptosis[63].

In recent years, the importance of immune cell infiltration in tumors has gradually been recognized[64, 65]. Blocking immune checkpoints has become a promising cancer treatment[66]. However, the relationship between the EGFR family and immune infiltration in gliomas has not been studied. In this paper, the timer database was used to analyze the relationship between EGFR family expression and immune penetration in gliomas. The expression of EGFR has a notably correlation with the level of B cell infiltration. ERBB2 expression was notably correlated with the level of macrophage infiltration. The expression of ERBB3 and ERBB4 was positively correlated with the level of CD4 + T cell infiltration. These correlations may suggest the potential mechanism of EGFR family to regulate immune cells of glioma. These findings indicate that the EGFR family plays a crucial role in the regulation of glioma immune cells.

In order to explore the potential mechanism of EGFR family involvement in glioma carcinogenesis, we constructed a PPI network and performed GO and KEGG analysis of the EGFR family on the basis of DAVID. The results showed that EGFR family interacting genes are mainly involved cell motility, which may affect integrin receptors and Rho family GTPases. Integrin receptors has been reported to interact with EGFR[67].

Moreover, Rho family GTPases play an important role in the interaction between EGFR family and their interactors. In summary, the interaction between integrin receptors/Rho family GTPases and the EGFR family may become a new antitumor therapy strategy by regulating signaling pathway[68].

Conclusion

This study systematically analyzed the EGFR family expression, mutation and prognosis of patients with glioma, and further understood the biological characteristics of glioma. Research indicates that EGFR family in glioma tissues may play an important role in the development of gliomas. The EGFR family can also be used as a molecular marker for glioblastoma. Through this research, the EGFR family may be potential biomarkers of the diagnosis and treatment of glioma and prognosis.

Abbreviations

EGFR: Epidermal growth factor receptor

GBM: glioblastoma

CNS: Brain and central nervous system

PPI: protein-protein interaction

MF: molecular function

CC: and cell composition

BP: biological process

OS: overall survival

DFS: disease free survival

DSS: disease-specific survival

PFS: Progression free survival

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets analysed for this study were obtained from the Oncomine database (https://www.oncomine.org/) and UCSC Xena website (https://xenabrowser.net/datapages/) and CGGA dataset (mRNAseq_325) (http://www.cgga.org.cn/index.jsp) and TIMER (https://cistrome.shinyapps.io/timer/) and cBioPortal (https://www.cbioportal.org/) and GeneMANIA database (http://www.genemania.org/) and DAVID (https://david.ncifcrf.gov/).

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Junfei S and Jun S conceived the study and participated in the study design, performance, coordination and manuscript writing. BX, WJ, ZYH, ZB and JJ performed the literature review and graphics production. Junfei S and Jun S revised the manuscript. All authors reviewed and approved the final manuscript.

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Figures

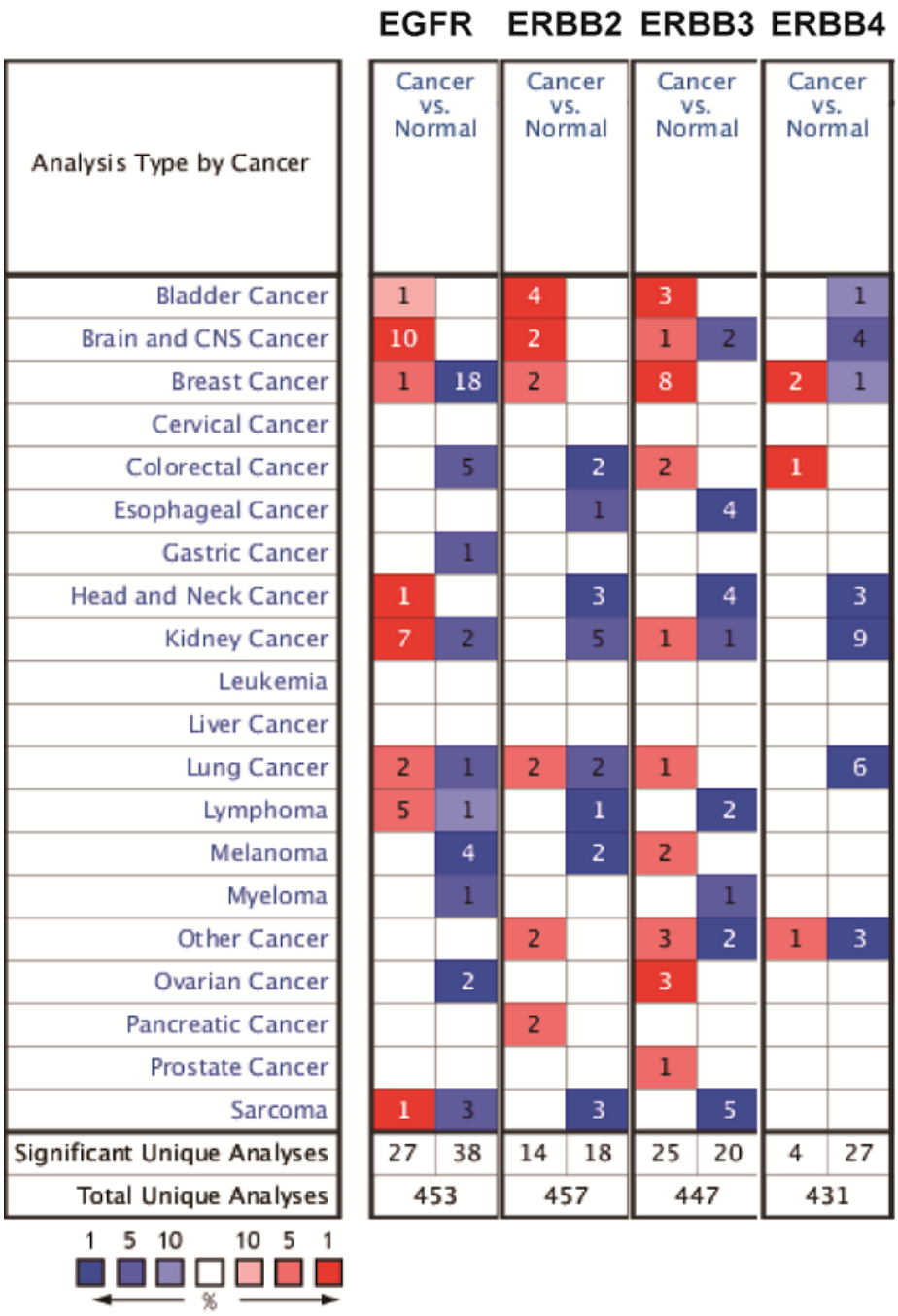

Figure 1

The expression of EGFR family in different cancers.

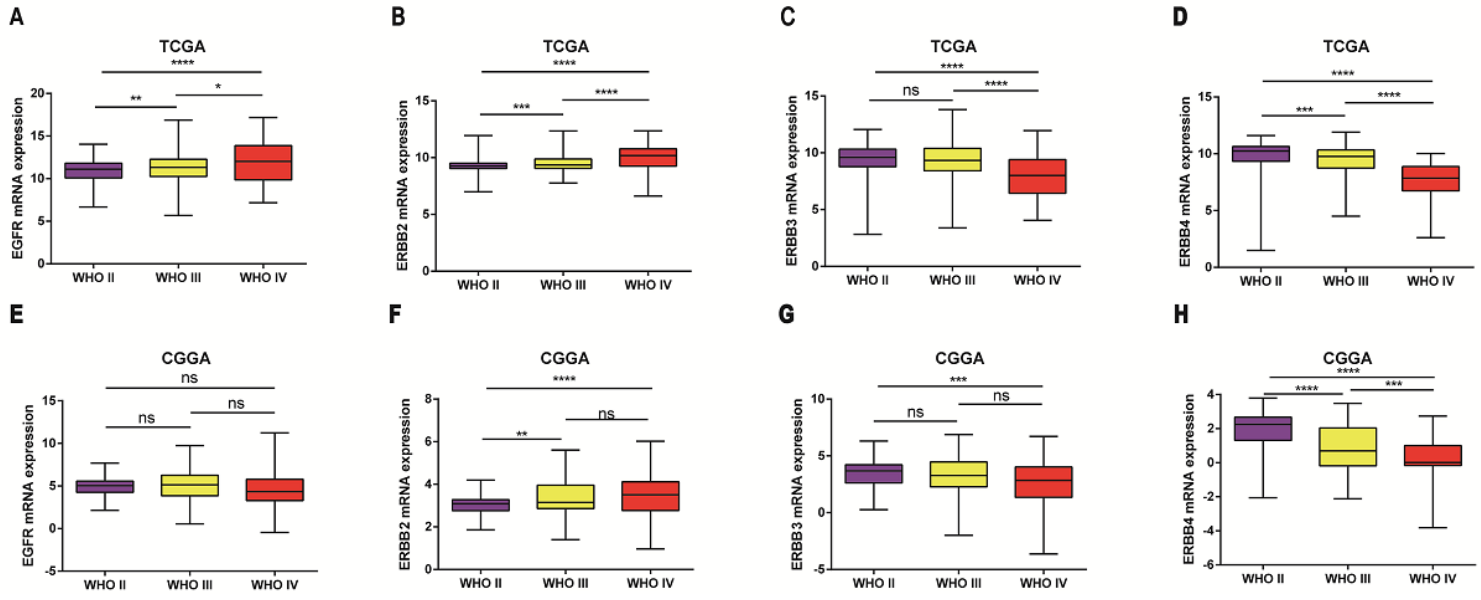

Figure 2

The expression level of EGFR family in different grades of glioma tissues (A, B, E and F) The mRNA expression levels of EGFR and ERBB2 were significantly high in GBM. (C, D, G, and H) The mRNA expression levels of ERBB3 and ERBB4 were significantly high in glioma (WHO II). * represents p <0.05, ** represents p <0.01, *** represents p <0.001, and **** represents p <0.0001.

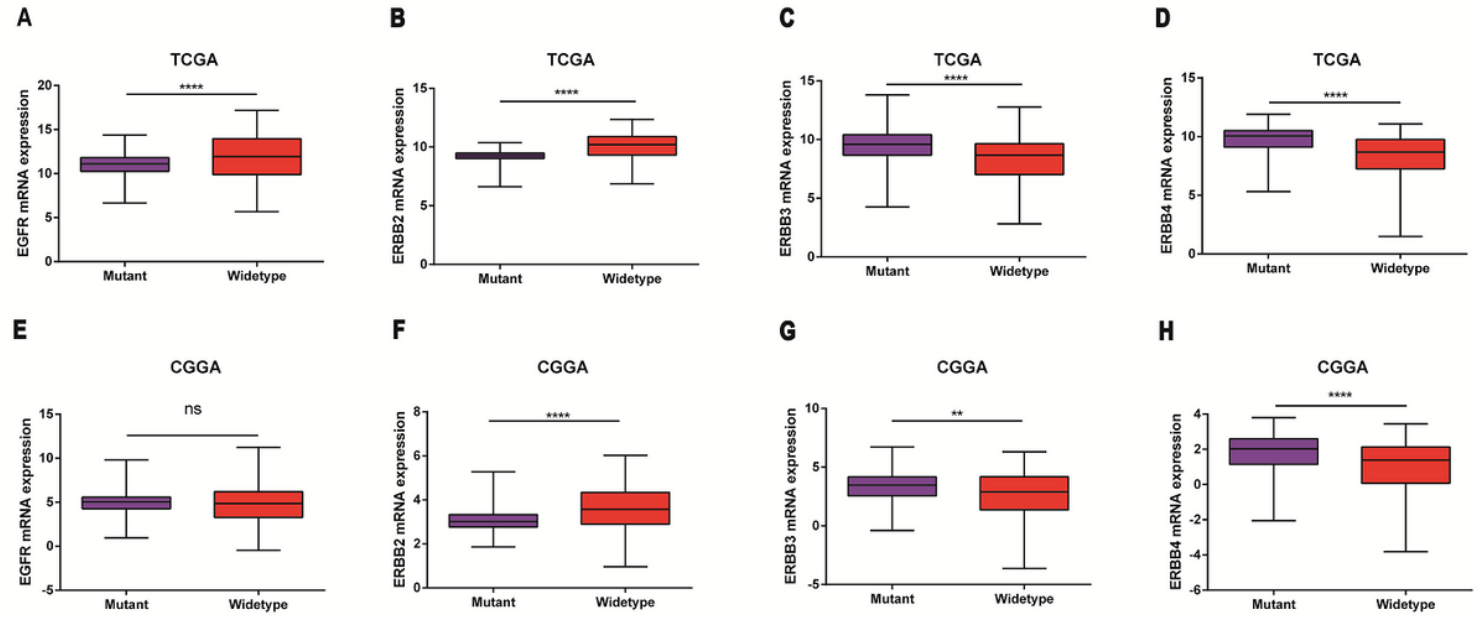

Figure 3

EGFR family expression was closely associated with IDH wild-type and mutation in glioma. (A, B, E and F) EGFR and ERBB2 was notably downregulated in IDH mutant glioma. (C, D, G and H) ERBB3 and ERBB4 was notably upregulated in IDH mutant glioma. * represents p <0.05, ** represents p <0.01, *** represents p <0.001, and **** represents p <0.0001.

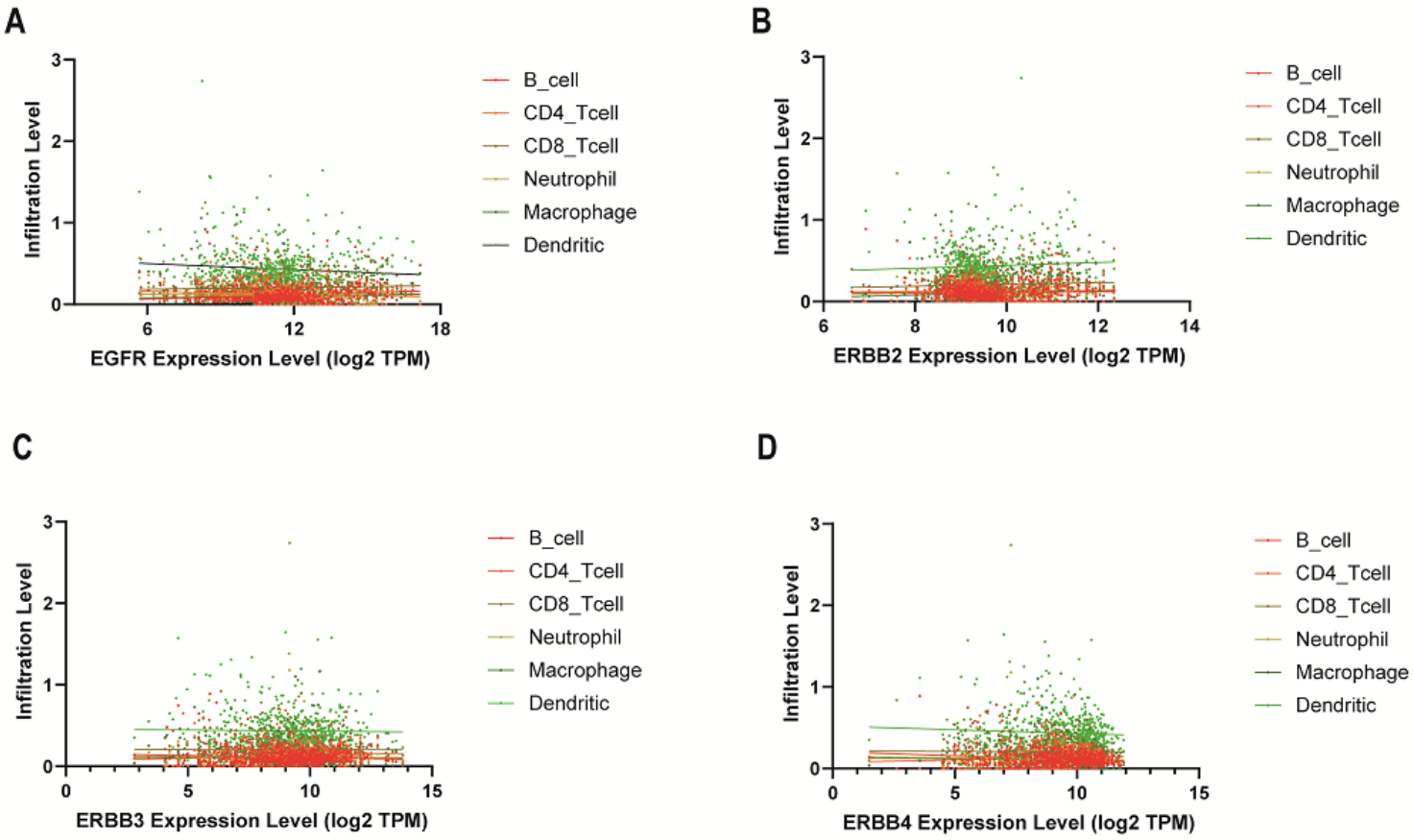

Figure 4

Correlation between transcription level of EGFR family and immune infiltration level in glioma. (A) The transcription level of EGFR was positively correlated with the level of B cells infiltration in tumor tissues. (B) The transcription level of ERBB2 EGFR was positively correlated with the level of macrophage infiltration in tumor tissues. (C and D) The transcriptional expression levels of ERBB3 and ERBB4 were positively correlated with the level of CD4+T cells infiltration in tumor tissues.

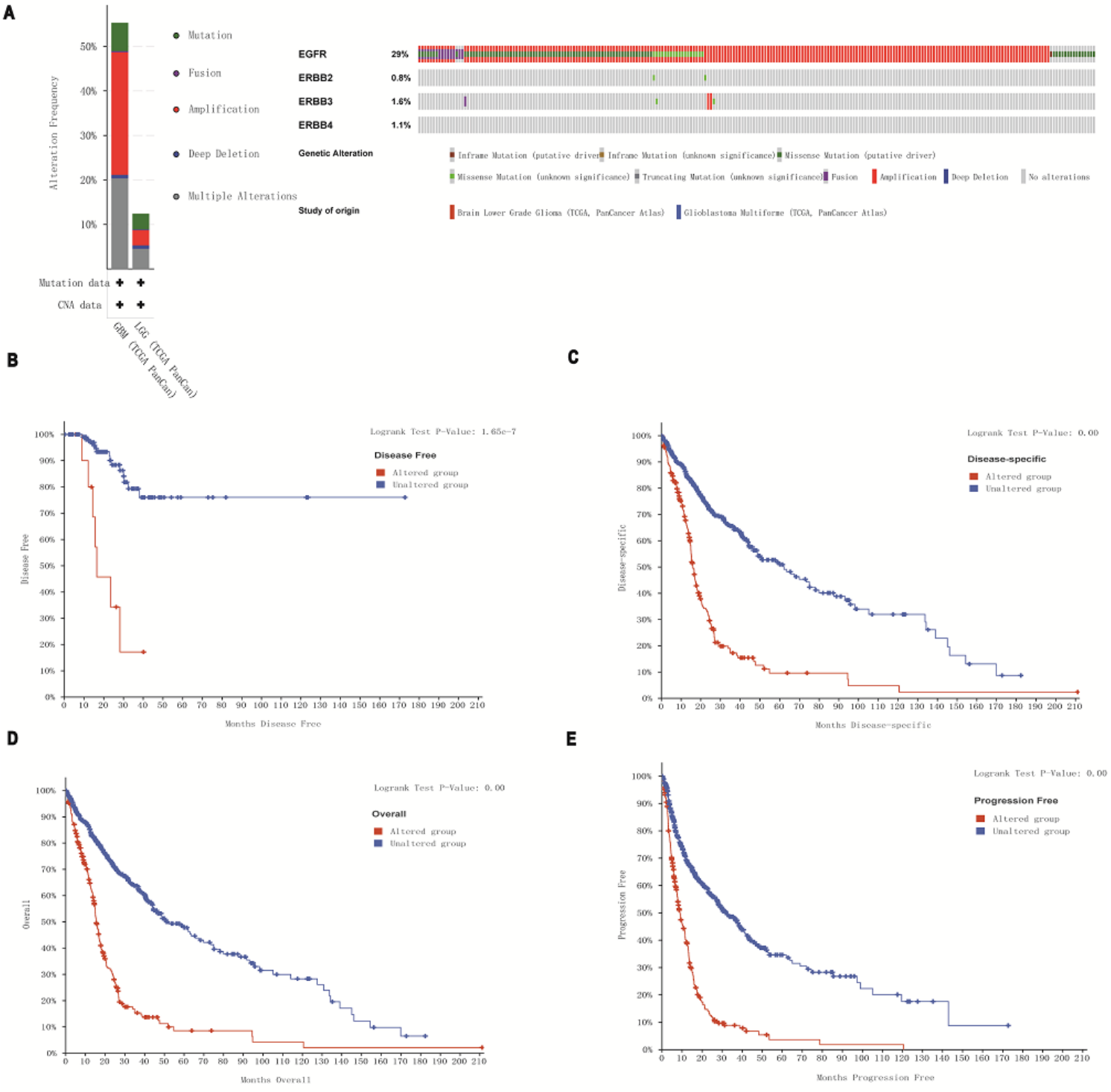

Figure 5

Relationship between EGFR family mutations and prognosis in gliomas. (A) The mutation rates of EGFR, ERBB2, ERBB3 and ERBB4 were 29%, 0.8%, 1.6% and 1.1%, respectively. (B, C, D and E) EGFR family mutations in glioma patients predicted poor OS, DFS, DS, and PFS.

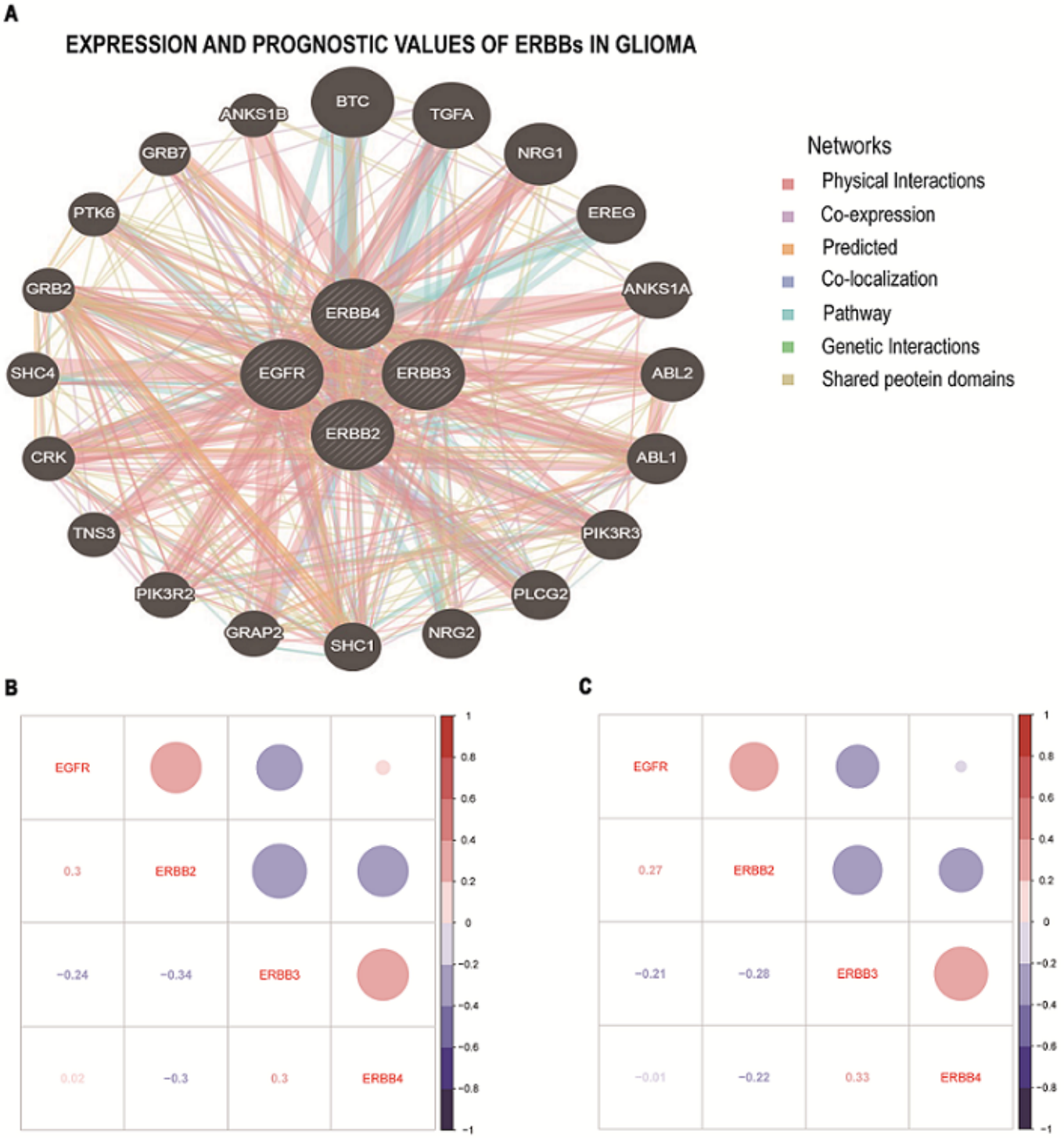

Figure 6

Predicted pathways and correlation of EGFR family gene expression in glioma. (A) PPI network for EGFR family was constructed in GeneMANIA. (B, C) Using Pearson's test to study the correlation between EGFR families.

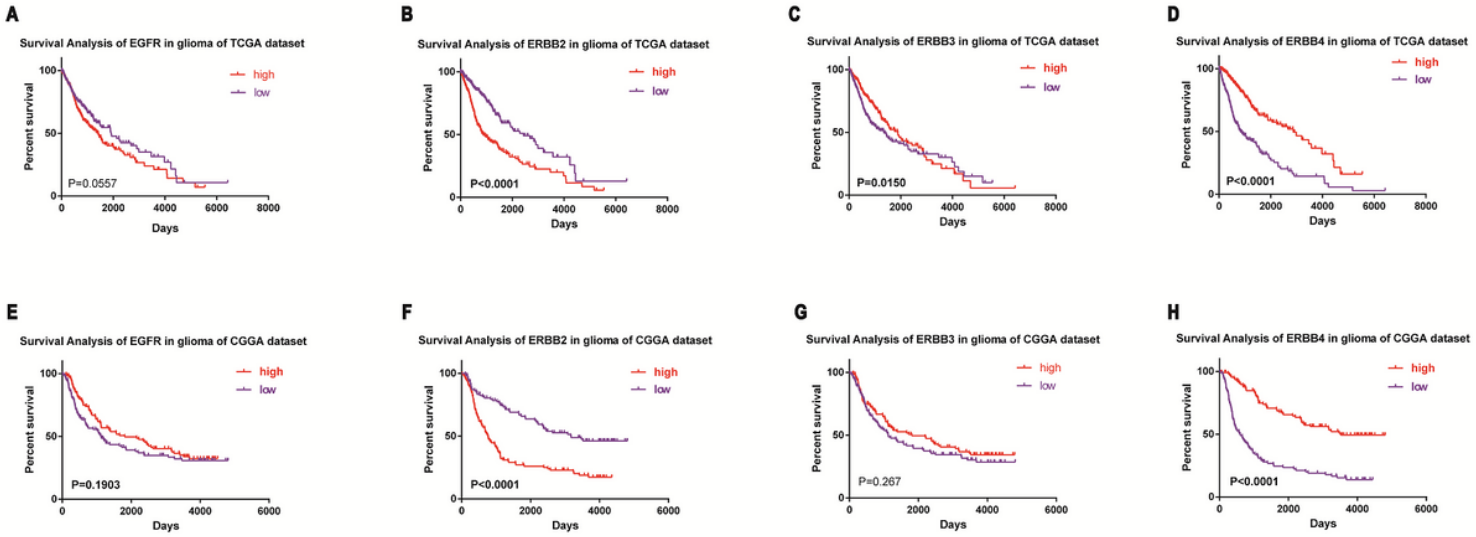

Figure 7

The prognostic value of EGFR family in glioma. (A, B, C and D) Overall survival of EGFR family in all grade glioma of TCGA dataset. (E, F, G and H) Overall survival of EGFR family in all grade glioma of CGGA dataset.