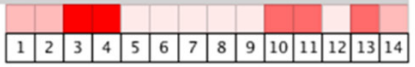
Comparison of IGFBP1 Across 14 Analyses

Over-expression / Copy Number Gain

Median Rank	p-Value	Gene
1148.5	0.020	IGFBP1



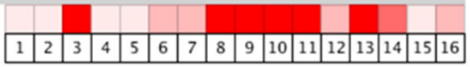
Legend

1. Anaplastic Astrocytoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
2. Anaplastic Oligodendroglioma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
3. Primary Glioblastoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
4. Secondary Glioblastoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
5. Glioblastoma vs. Normal
   Lee Brain, Cancer Cell, 2006
6. Anaplastic Astrocytoma vs. Normal
   Sun Brain, Cancer Cell, 2006
7. Glioblastoma vs. Normal
   Sun Brain, Cancer Cell, 2006
8. Oligodendroglioma vs. Normal
   Sun Brain, Cancer Cell, 2006
9. Brain Glioblastoma vs. Normal
   TCGA Brain, No Associated Paper, 2013
10. Brain Astrocytoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
11. Brain Glioblastoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
12. Brain Oligodendroglioma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
13. Glioblastoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
14. Oligoastrocytoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013

Comparison of IGFBP2 Across 16 Analyses

Over-expression / Copy Number Gain

Median Rank	p-Value	Gene
434.0	0.006	IGFBP2



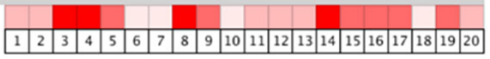
Legend

1. Anaplastic Oligodendroglioma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
2. Primary Glioblastoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
3. Glioblastoma vs. Normal
   Bredel Brain 2, Cancer Res, 2005
4. Anaplastic Oligoastrocytoma vs. Normal
   French Brain, Cancer Res, 2006
5. Anaplastic Oligodendroglioma vs. Normal
   French Brain, Cancer Res, 2006
6. Pilocytic Astrocytoma vs. Normal
   Gutmann Brain, Cancer Res, 2002
7. Glioblastoma vs. Normal
   Murat Brain, J Clin Oncol, 2008
8. Classic Medulloblastoma vs. Normal
   Pomeroy Brain, Nature, 2002
9. Desmoplastic Medulloblastoma vs. Normal
   Pomeroy Brain, Nature, 2002
10. Astrocytoma vs. Normal
    Rickman Brain, Cancer Res, 2001
11. Glioblastoma vs. Normal
    Shai Brain, Oncogene, 2003
12. Anaplastic Astrocytoma vs. Normal
    Sun Brain, Cancer Cell, 2006
13. Glioblastoma vs. Normal
    Sun Brain, Cancer Cell, 2006
14. Brain Glioblastoma vs. Normal
    TCGA Brain, No Associated Paper, 2013
15. Brain Glioblastoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
16. Meningioma vs. Normal
    Watson Brain, Am J Pathol, 2002

Comparison of IGFBP3 Across 20 Analyses

Over-expression / Copy Number Gain

Median Rank	p-Value	Gene
674.5	1.73E-8	IGFBP3



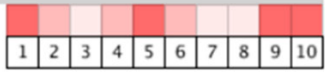
Legend

1. Anaplastic Astrocytoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
2. Anaplastic Oligodendroglioma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
3. Primary Glioblastoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
4. Secondary Glioblastoma vs. Normal
   Beroukhim Brain, Proc Natl Acad Sci U S A, 2007
5. Glioblastoma vs. Normal
   Bredel Brain 2, Cancer Res, 2005
6. Anaplastic Oligoastrocytoma vs. Normal
   French Brain, Cancer Res, 2006
7. Anaplastic Oligodendroglioma vs. Normal
   French Brain, Cancer Res, 2006
8. Pilocytic Astrocytoma vs. Normal
   Gutmann Brain, Cancer Res, 2002
9. Glioblastoma vs. Normal
   Lee Brain, Cancer Cell, 2006
10. Glioblastoma vs. Normal
    Liang Brain, Proc Natl Acad Sci U S A, 2005
11. Glioblastoma vs. Normal
    Murat Brain, J Clin Oncol, 2008
12. Astrocytoma vs. Normal
    Rickman Brain, Cancer Res, 2001
13. Glioblastoma vs. Normal
    Shai Brain, Oncogene, 2003
14. Glioblastoma vs. Normal
    Sun Brain, Cancer Cell, 2006
15. Brain Glioblastoma vs. Normal
    TCGA Brain, No Associated Paper, 2013
16. Brain Astrocytoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
17. Brain Glioblastoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
18. Brain Oligodendroglioma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
19. Glioblastoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013
20. Oligoastrocytoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013

Comparison of IGFBP4 Across 10 Analyses

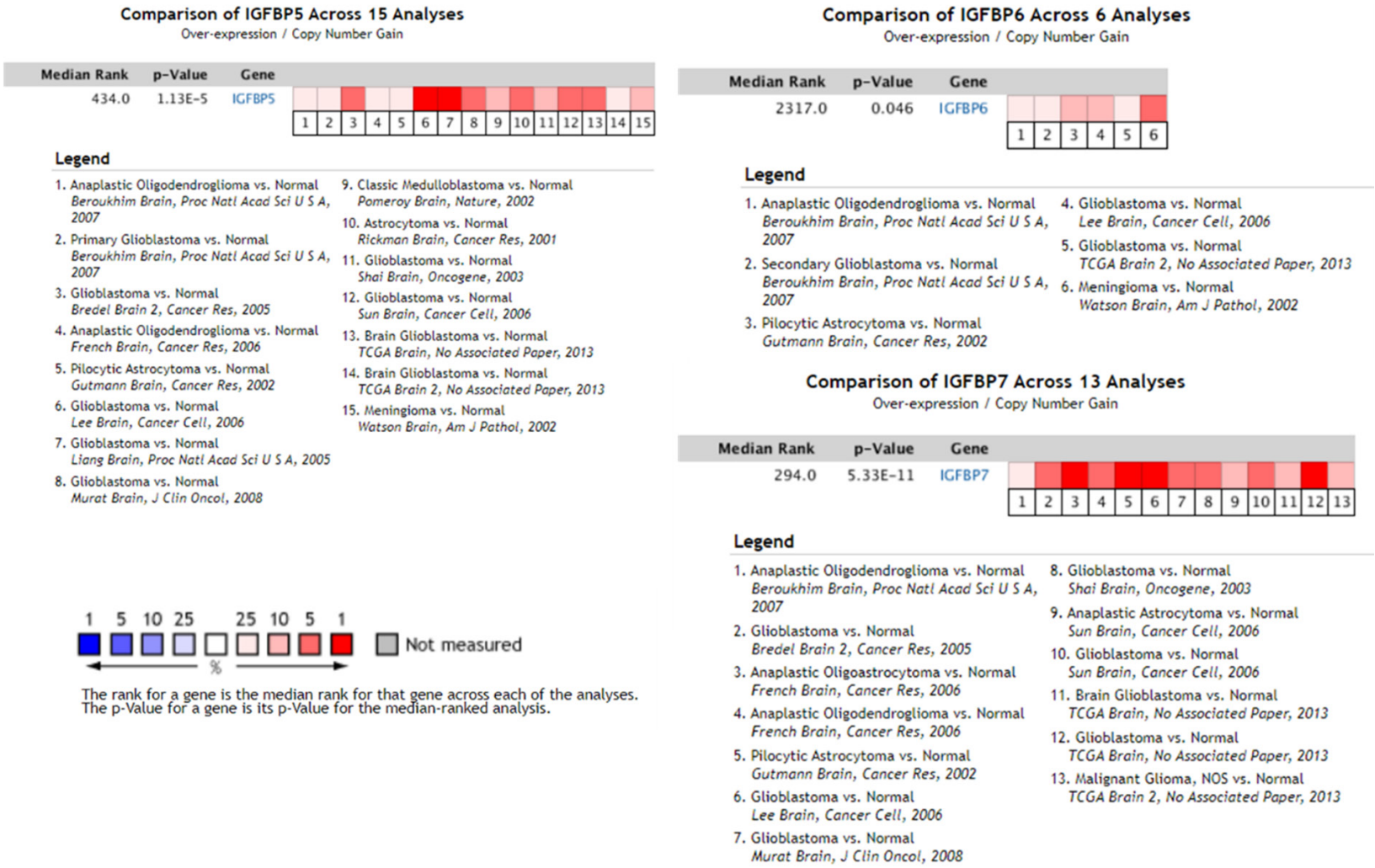
Over-expression / Copy Number Gain

Median Rank	p-Value	Gene
774.5	1.15E-6	IGFBP4

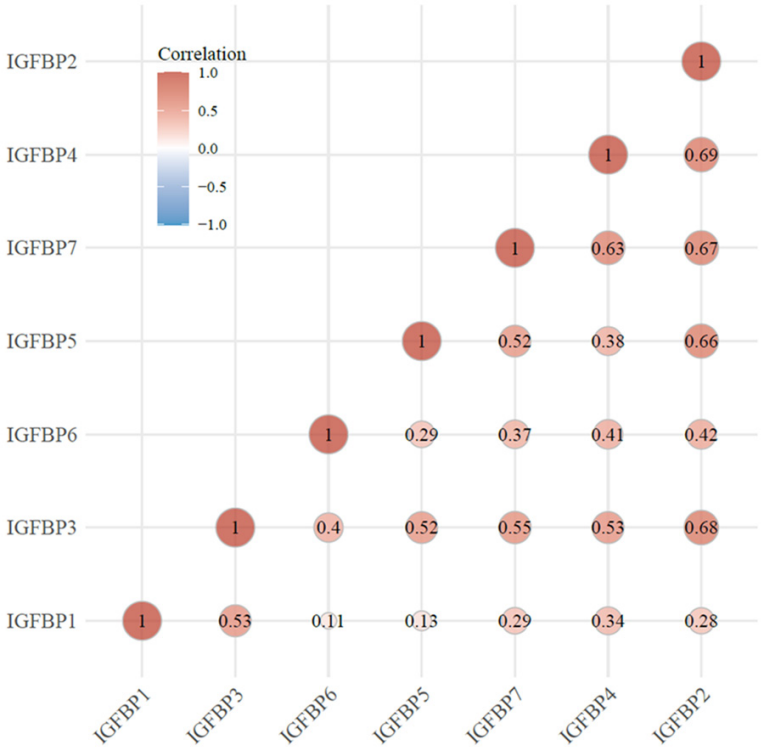


Legend

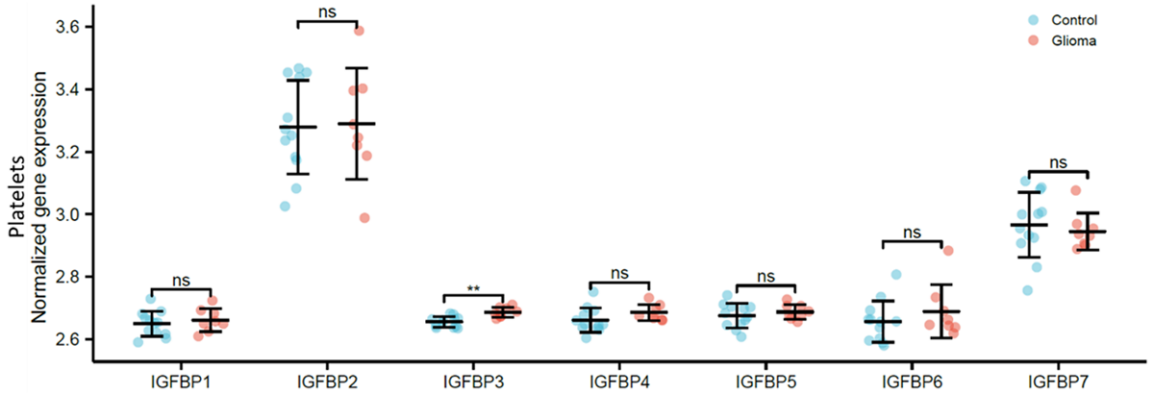
1. Anaplastic Oligodendroglioma vs. Normal
   French Brain, Cancer Res, 2006
2. Pilocytic Astrocytoma vs. Normal
   Gutmann Brain, Cancer Res, 2002
3. Glioblastoma vs. Normal
   Lee Brain, Cancer Cell, 2006
4. Astrocytoma vs. Normal
   Rickman Brain, Cancer Res, 2001
5. Glioblastoma vs. Normal
   Shai Brain, Oncogene, 2003
6. Glioblastoma vs. Normal
   Sun Brain, Cancer Cell, 2006
7. Brain Glioblastoma vs. Normal
   TCGA Brain, No Associated Paper, 2013
8. Glioblastoma vs. Normal
   TCGA Brain, No Associated Paper, 2013
9. Brain Oligodendroglioma vs. Normal
   TCGA Brain 2, No Associated Paper, 2013
10. Oligoastrocytoma vs. Normal
    TCGA Brain 2, No Associated Paper, 2013



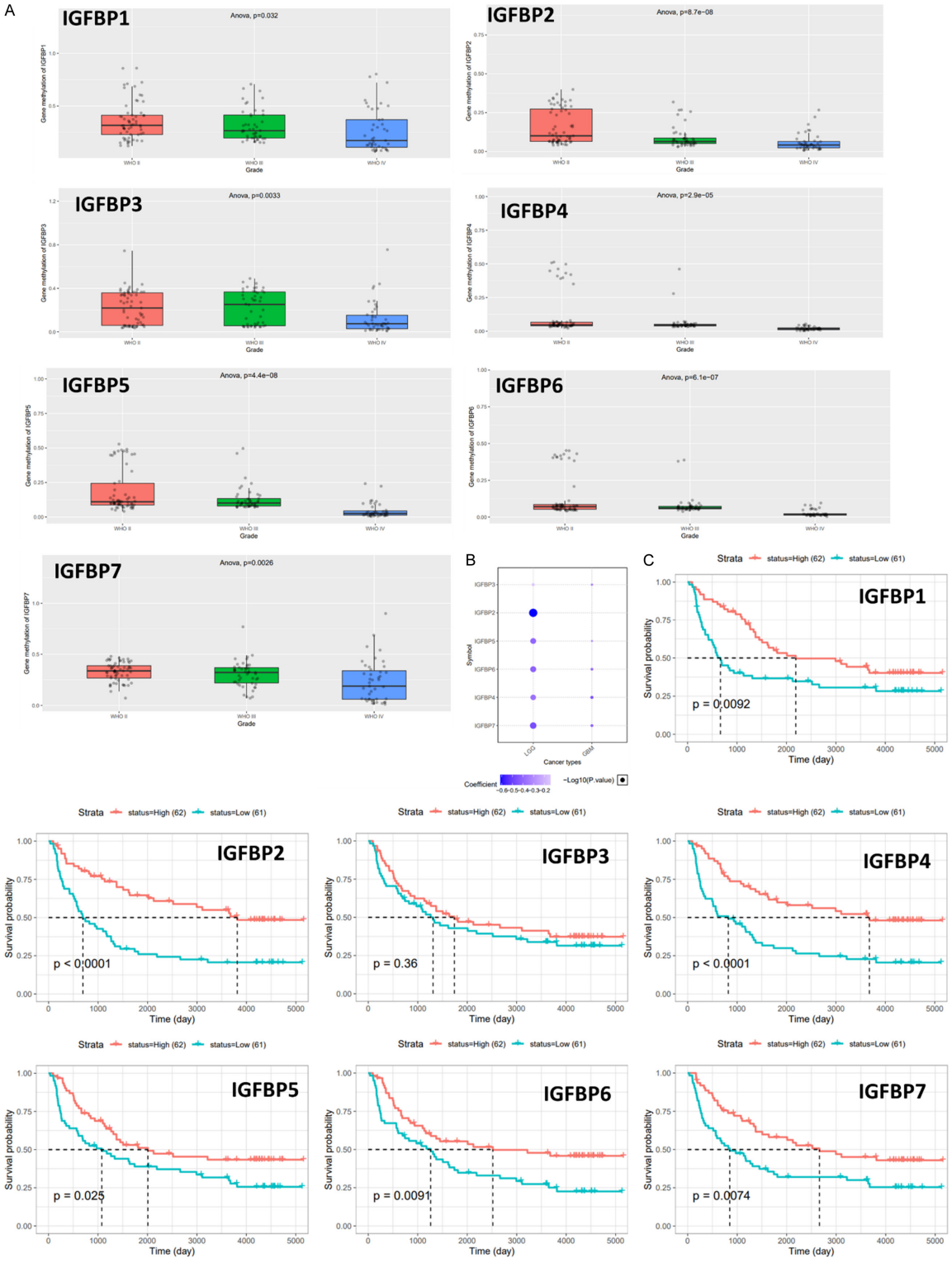
Supplementary Figure 1. The IGFBP mRNA overexpression/gene copy number gain in glioma compared to normal brain tissues across analyses. All the data were accessed and analyzed using Oncomine.



Supplementary Figure 2. mRNA expression correlations of IGFBPs in glioma. TCGA (LGG+GBM) mRNA expression cohorts were analyzed.

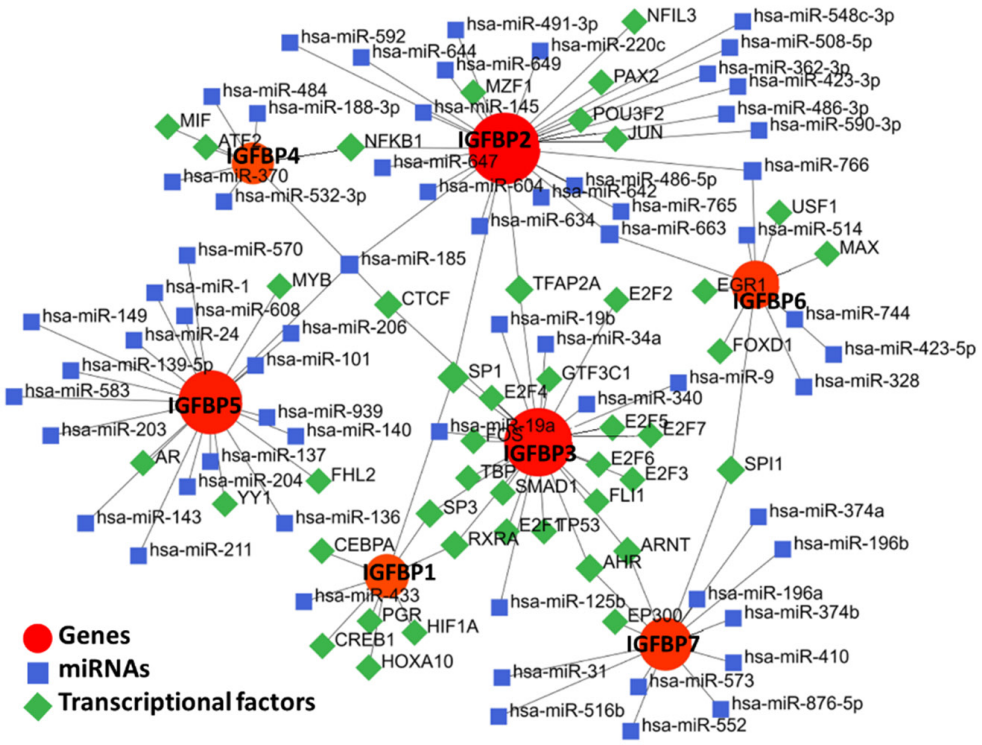


Supplementary Figure 3. Expression of IGFBPs in platelets from glioma patients or healthy donors. GSE31095 cohort was analyzed.

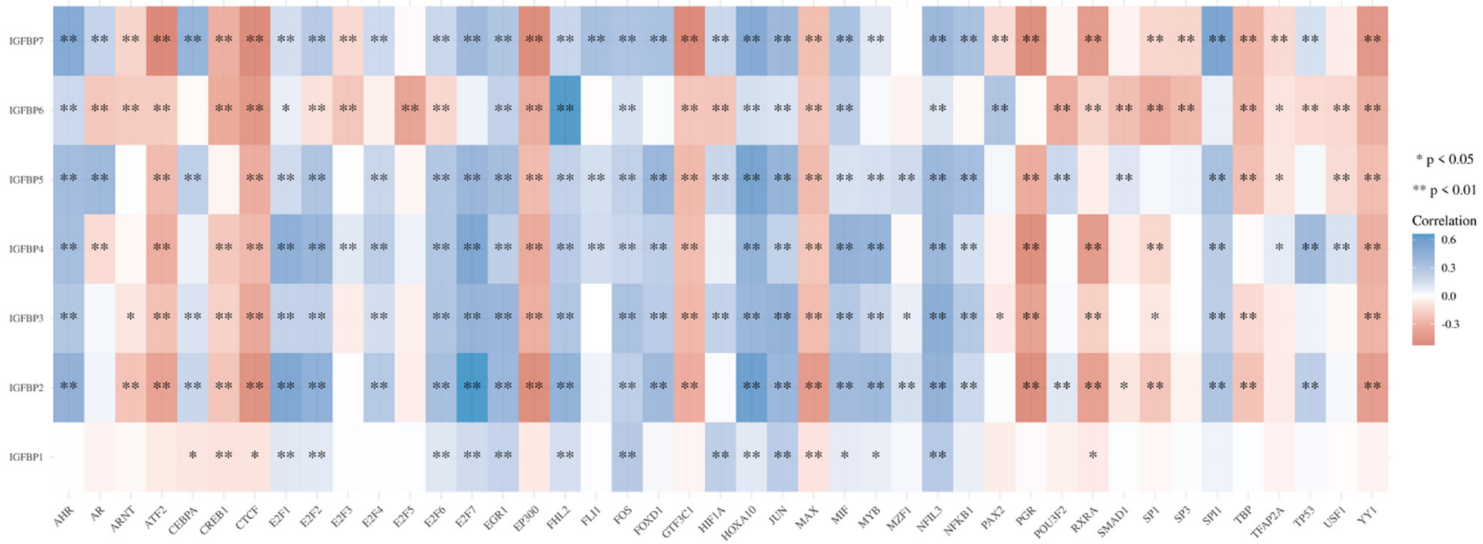


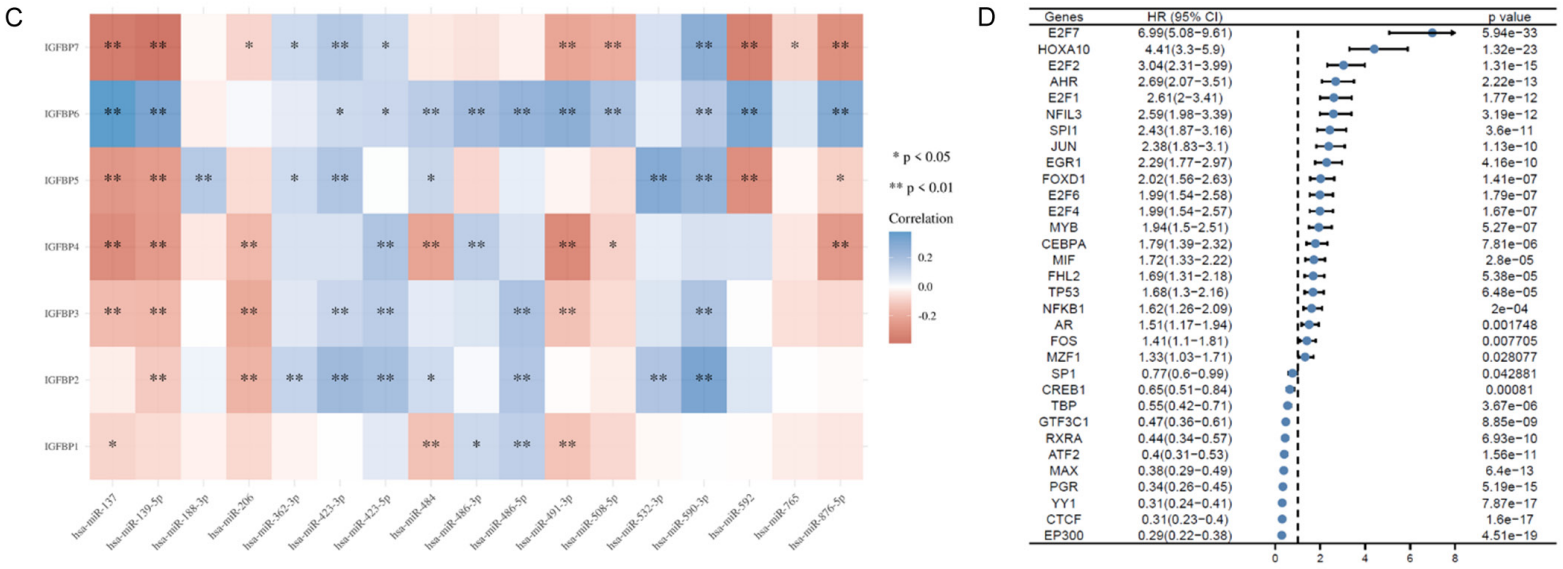
Supplementary Figure 4. Methylation of IGFBPs in glioma. CGGA Methyl_159 cohort was analyzed. A. Methylation levels of IGFBPs in different grades of glioma (grade 2-4). B. Correlation of methylation and IGFBP mRNA expression. C. Overall survival KM plots and log-rank analysis of glioma with different methylation of IGFBPs.

A

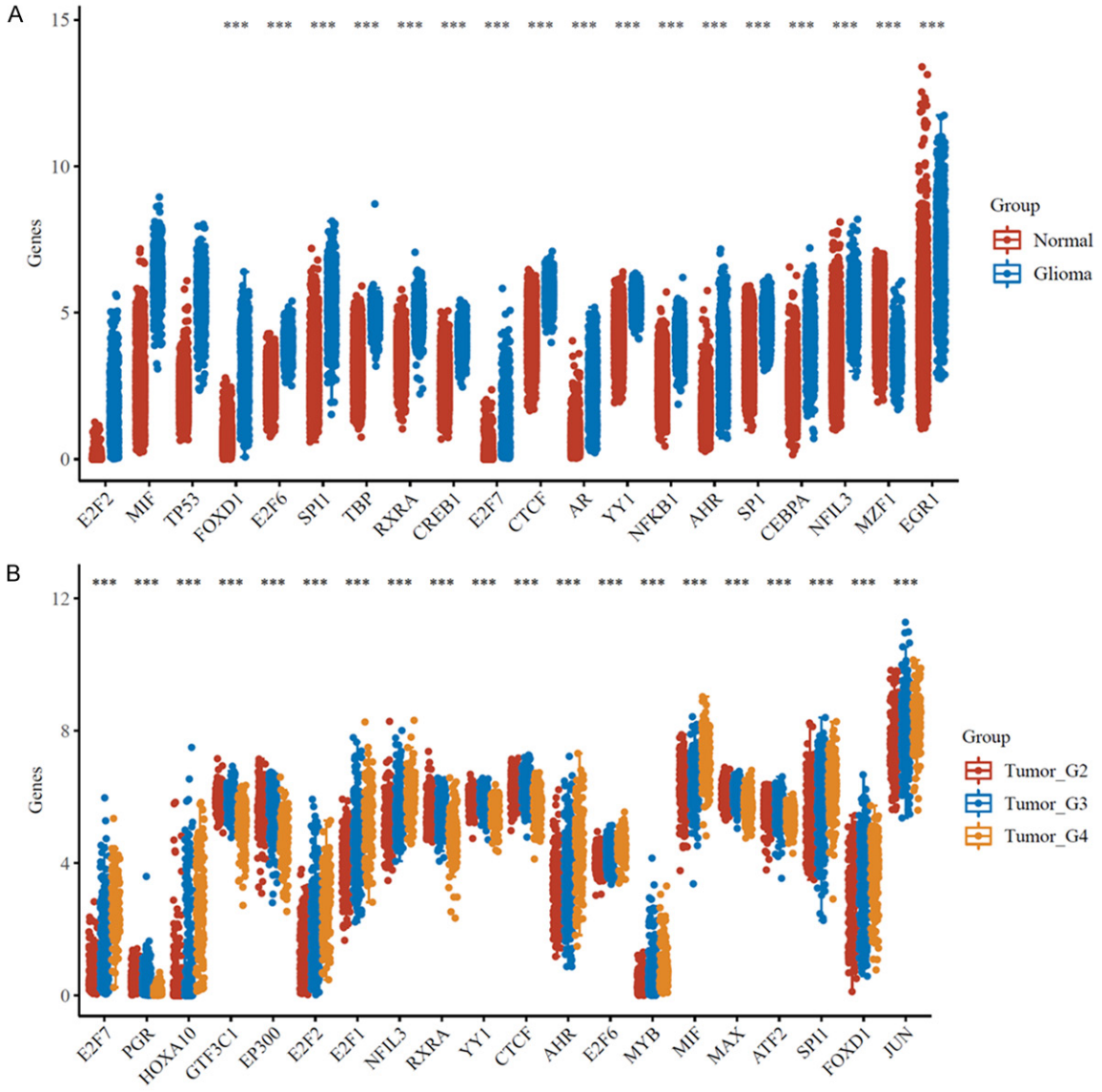

IGFBP1
IGFBP2
IGFBP3
IGFBP4
IGFBP5
IGFBP6
IGFBP7
hsa-miR-592
hsa-miR-491-3p
NFIL3
hsa-miR-548c-3p
hsa-miR-644
hsa-miR-220c
hsa-miR-508-5p
hsa-miR-649
PAX2
hsa-miR-362-3p
MZF1
hsa-miR-423-3p
hsa-miR-484
hsa-miR-188-3p
hsa-miR-145
POU3F2
hsa-miR-486-3p
MIF
ATF2
NFKB1
JUN
hsa-miR-590-3p
hsa-miR-647
hsa-miR-766
hsa-miR-370
hsa-miR-532-3p
hsa-miR-604
hsa-miR-642
hsa-miR-486-5p
hsa-miR-765
USF1
hsa-miR-634
hsa-miR-663
hsa-miR-514
MAX
hsa-miR-570
hsa-miR-185
hsa-miR-1
MYB
CTCF
TFAP2A
E2F2
EGR1
hsa-miR-149
hsa-miR-608
hsa-miR-19b
hsa-miR-744
hsa-miR-24
hsa-miR-206
hsa-miR-34a
FOXD1
hsa-miR-423-5p
hsa-miR-139-5p
hsa-miR-101
SP1
GTF3C1
hsa-miR-9
hsa-miR-328
hsa-miR-583
E2F4
hsa-miR-340
hsa-miR-939
E2F5
E2F7
hsa-miR-203
hsa-miR-140
hsa-miR-19a
E2F6
AR
hsa-miR-137
TBP
E2F3
SPI1
hsa-miR-204
FHL2
SMAD1
FLI1
YY1
hsa-miR-143
hsa-miR-136
SP3
hsa-miR-374a
E2F1
TP53
CEBPA
RXRA
ARNT
hsa-miR-196b
hsa-miR-211
AHR
hsa-miR-433
hsa-miR-125b
hsa-miR-196a
PGR
EP300
hsa-miR-374b
HIF1A
CREB1
hsa-miR-410
HOXA10
hsa-miR-31
hsa-miR-573
hsa-miR-516b
hsa-miR-876-5p
hsa-miR-552
Genes
miRNAs
Transcriptional factors

B


IGFBP7
IGFBP6
IGFBP5
IGFBP4
IGFBP3
IGFBP2
IGFBP1
AHR AR ARNT ATF2 CEBPA CREB1 CTCF E2F1 E2F2 E2F3 E2F4 E2F5 E2F6 E2F7 EGR1 EP300 FHL2 FLI1 FOS FOXD1 GTF3C1 HIF1A HOXA10 JUN MAX MIF MYB MZF1 NFIL3 NFKB1 PAX2 PGR POU3F2 RXRA SMAD1 SP1 SP3 SPI1 TBP TFAP2A TP53 USF1 YY1
* p < 0.05
** p < 0.01
Correlation
0.6
0.3
0.0
-0.3



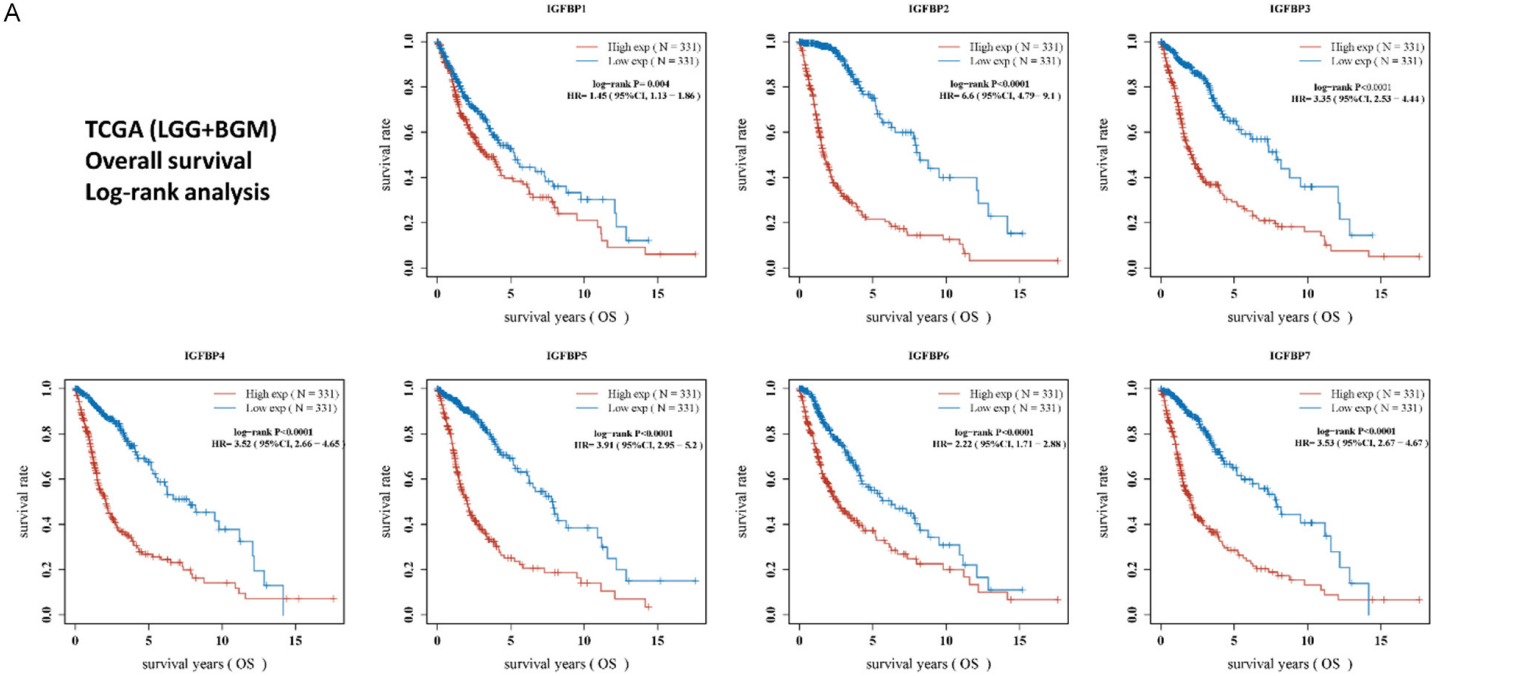
Supplementary Figure 5. Regulation of IGFBP expression. TCGA (LGG+GBM) RNA expression cohort was analyzed. A. Gene-miRNA-transcriptional factor coregulation network of IGFBPs constructed by RegNetwork. B. Correlation of IGFBPs and transcriptional factor mRNA expression. C. Correlation of IGFBPs and miRNA expression. Genes that were not detected in the cohort were excluded. D. Transcriptional factors for IGFBP associated with the survival of glioma patients.



Supplementary Figure 6. Expression of transcription factors of IGFBP associated with the survival of glioma patients. TCGA (LGG+GBM) mRNA expression cohort was analyzed. A. Expression of IGFBPs in glioma and normal brain tissues. B. Expression of transcription factors of IGFBPs associated with survival of glioma patients in grade 2-4 glioma (G2-4).

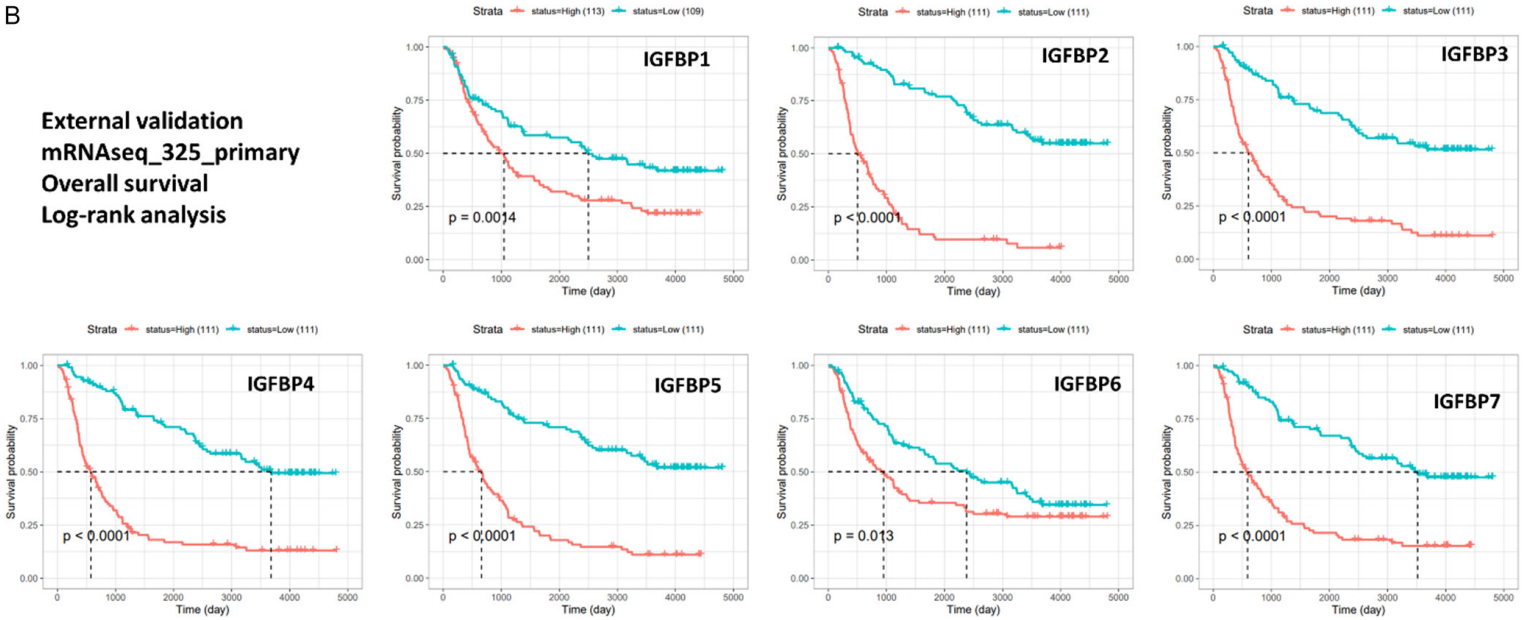
A

TCGA (LGG+BGM)
Overall survival
Log-rank analysis

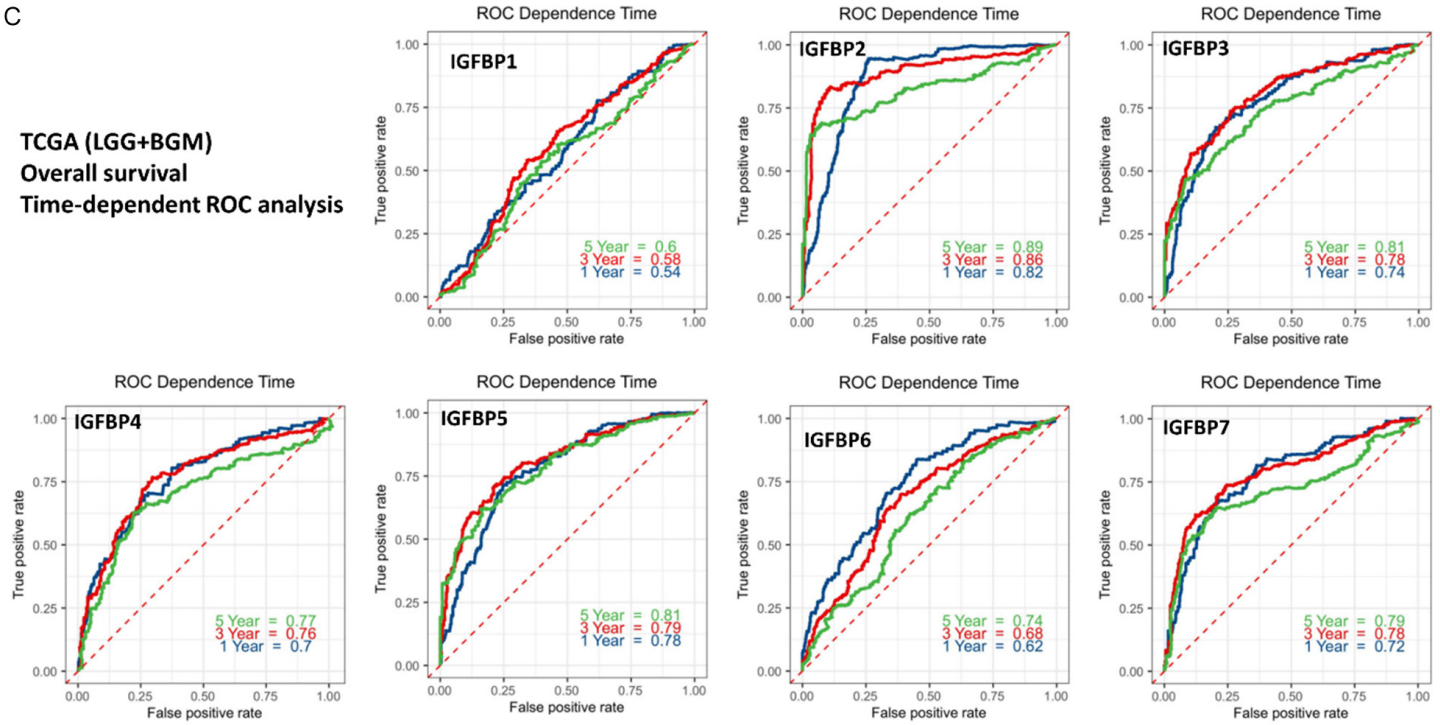


B

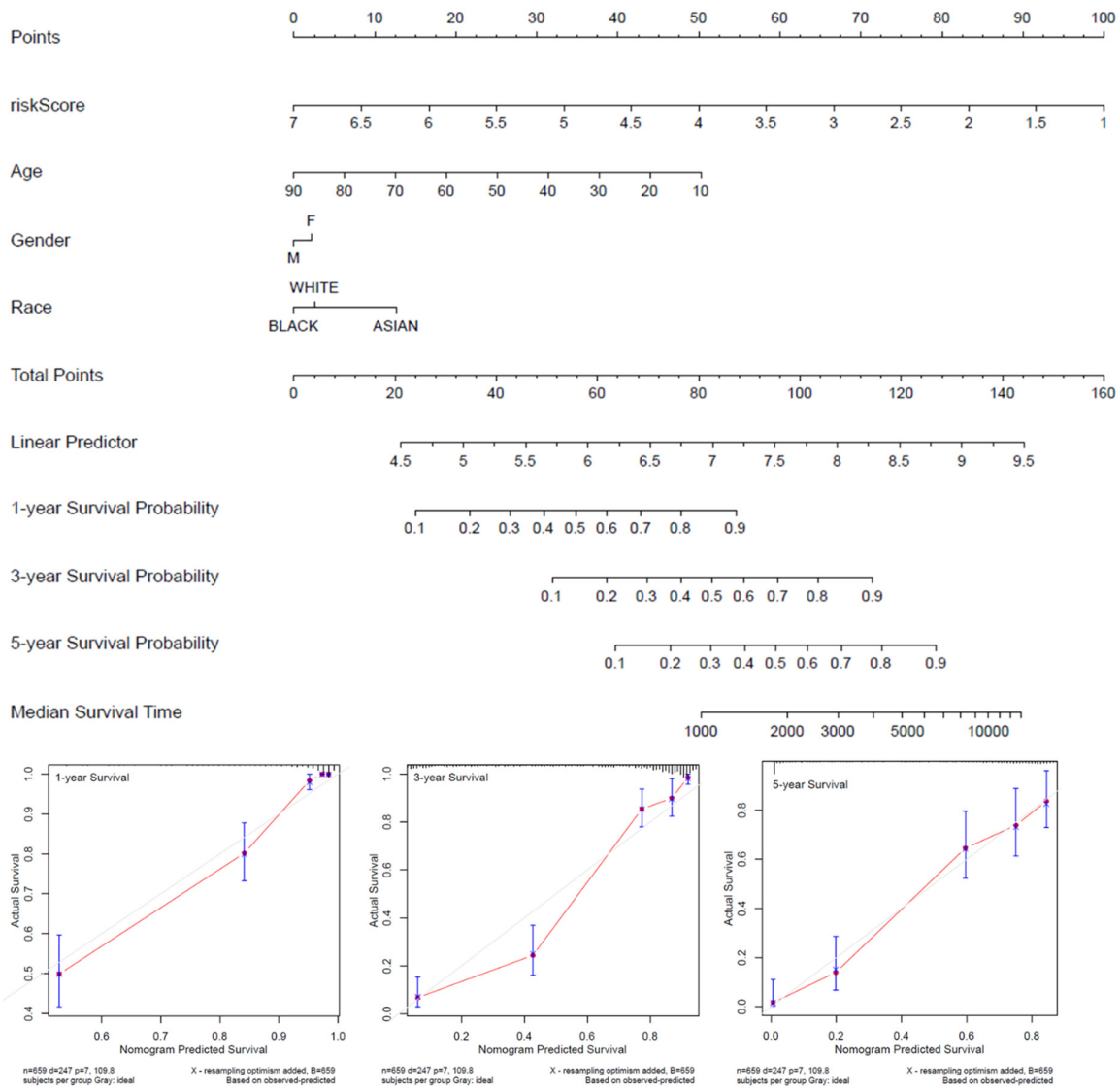
External validation
mRNAseq_325_primary
Overall survival
Log-rank analysis



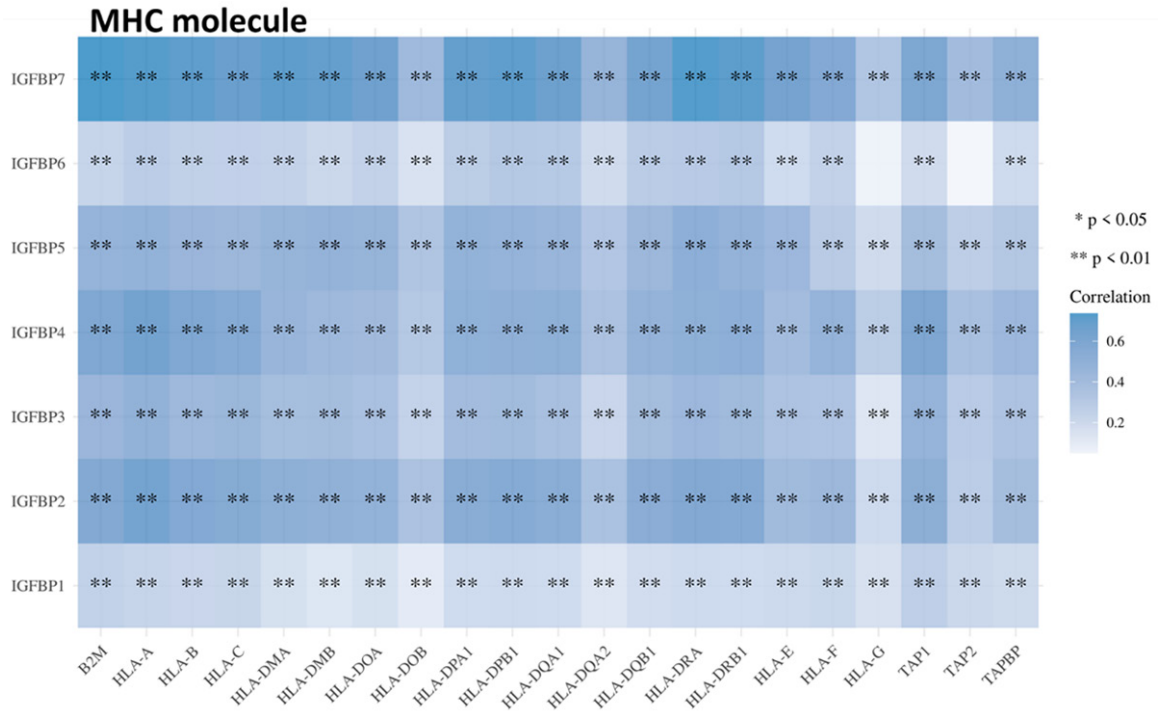
C



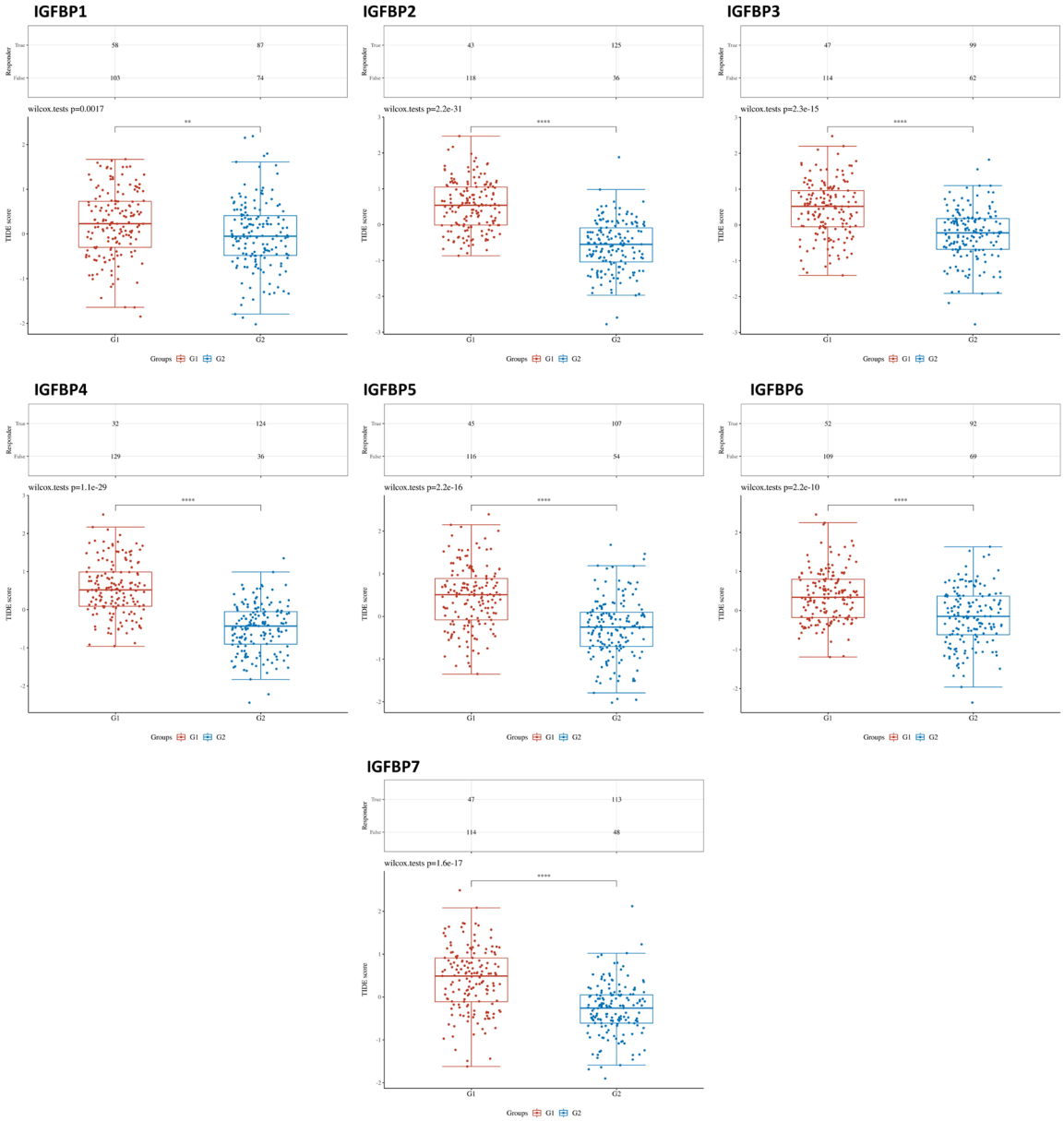
Supplementary Figure 7. Prognostic value of IGFBPs for glioma. A. Overall survival K-M plots and log-rank analysis of IGFBPs in glioma. TCGA (LGG+GBM) mRNA expression cohort was analyzed. B. Overall survival K-M plots and log-rank validation of IGFBPs in glioma. CGGA mRNAseq_325_primary mRNA expression cohort was analyzed to validate the prognostic value of IGFBPs for glioma. C. Overall survival time-dependent ROC curve of IGFBPs for glioma patients. TCGA (LGG+GBM) mRNA expression cohort was analyzed.



Supplementary Figure 8. Prognostic nomogram and calibration curves based on the LASSO regression model. TCGA (LGG+GBM) mRNA expression cohort was used to calibrate the model.

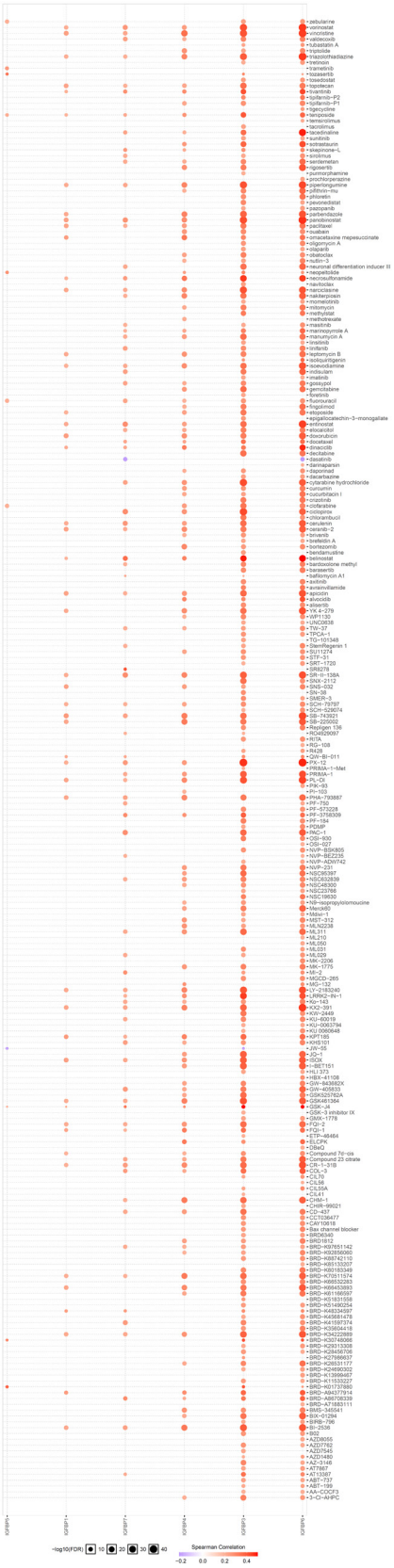


Supplementary Figure 9. Correlations of expression of MHC molecule and expression of IGFBPs. TCGA (LGG+GBM) mRNA expression cohort was analyzed.

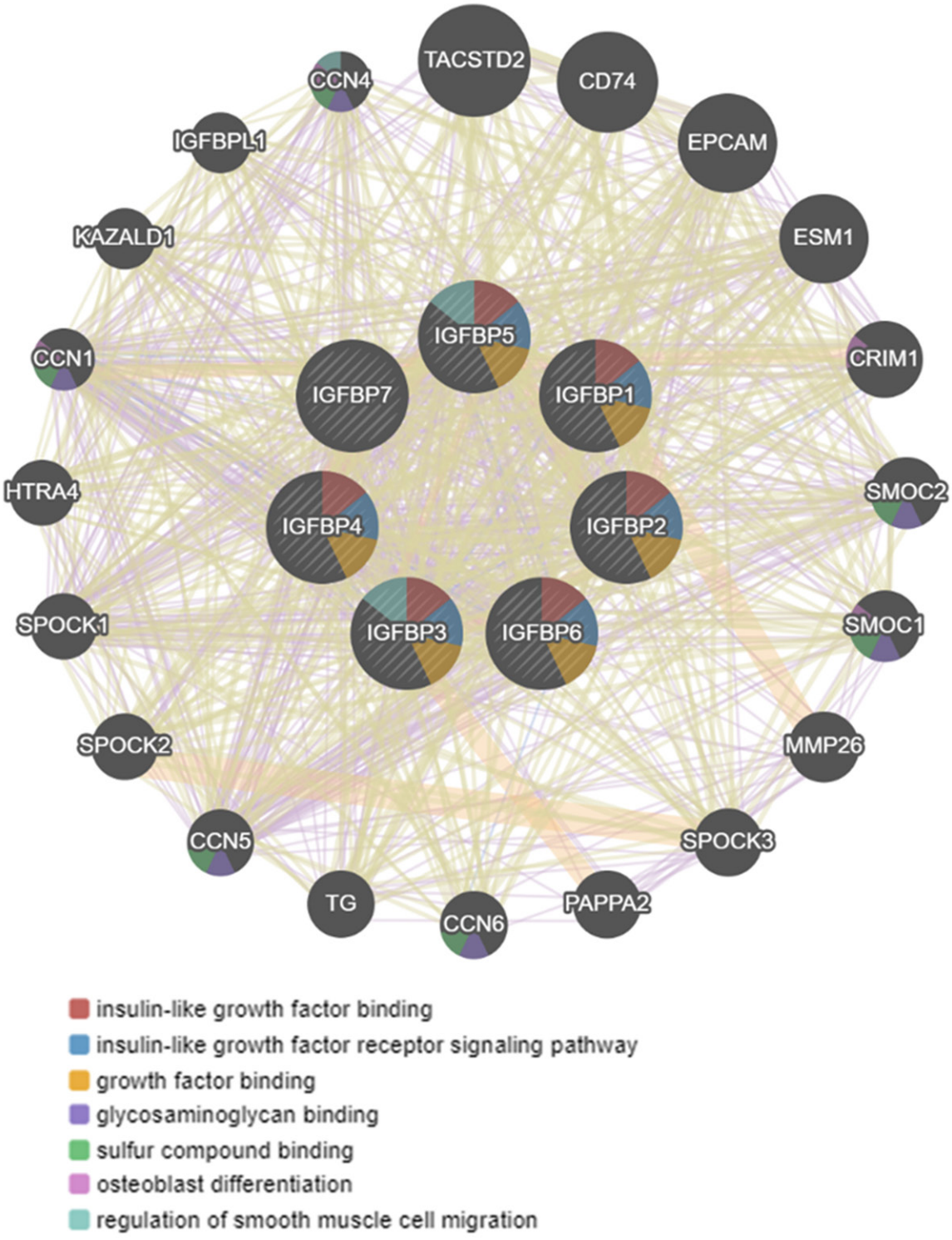


Supplementary Figure 10. Predictive value of IGFBPs for immune therapy. TCGA (LGG+GBM) mRNA expression cohort was analyzed. IGFBP high (G1, 75-100%) and low (G2, 0-25%) groups were compared. The Immune checkpoint blockade (ICB) response was predicted using the Tumor Immune Dysfunction and Exclusion (TIDE) algorithm.

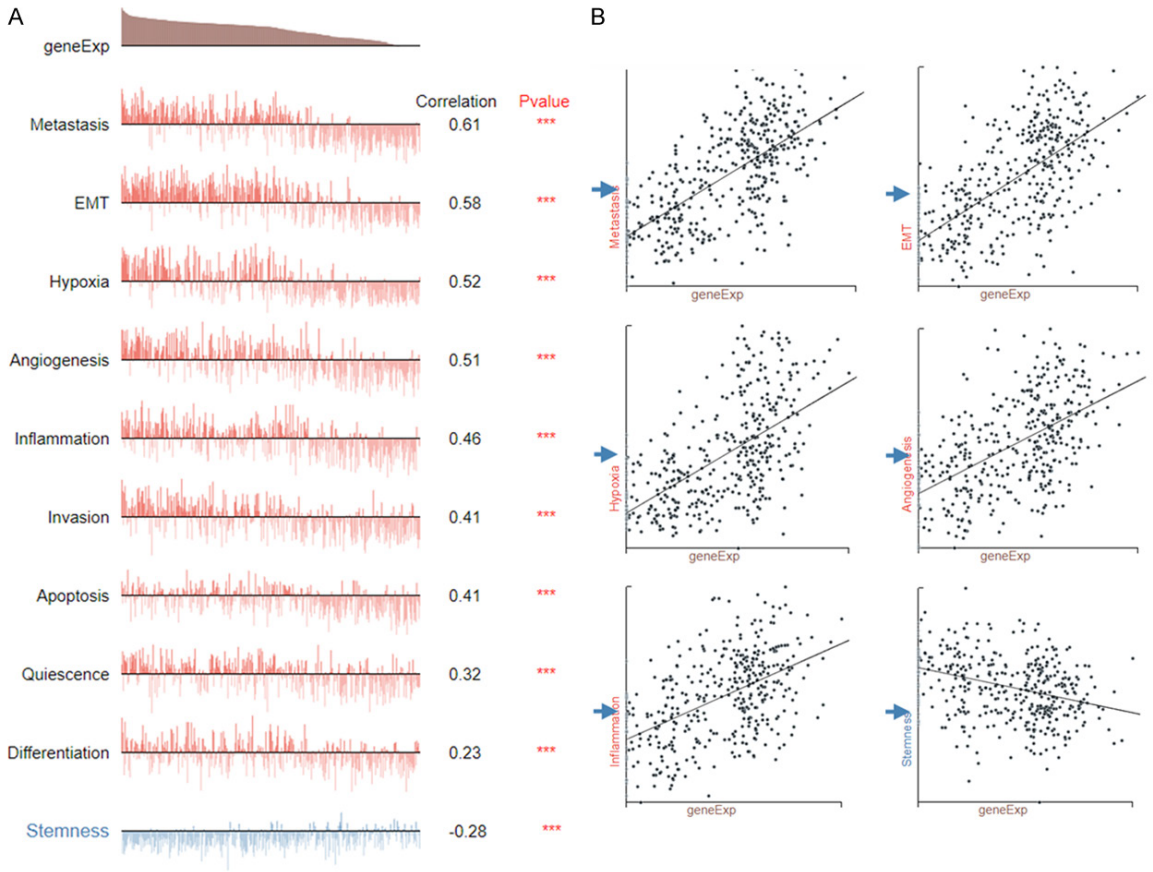
Supplementary Figure 11. Predictive value of IGFBPs for GDSC drug therapy in cancers. The GSCALite was used to evaluate the area under the dose-response curve (AUC) values for drugs and gene expression profiles of IGFBPs in different cancer cell lines. Drug sensitivity and gene expression profiling data of cancer cell lines in GDSC are integrated for investigation. The expression of each gene in the gene set was assessed by Spearman correlation analysis with the small molecule/drug sensitivity (IC50).



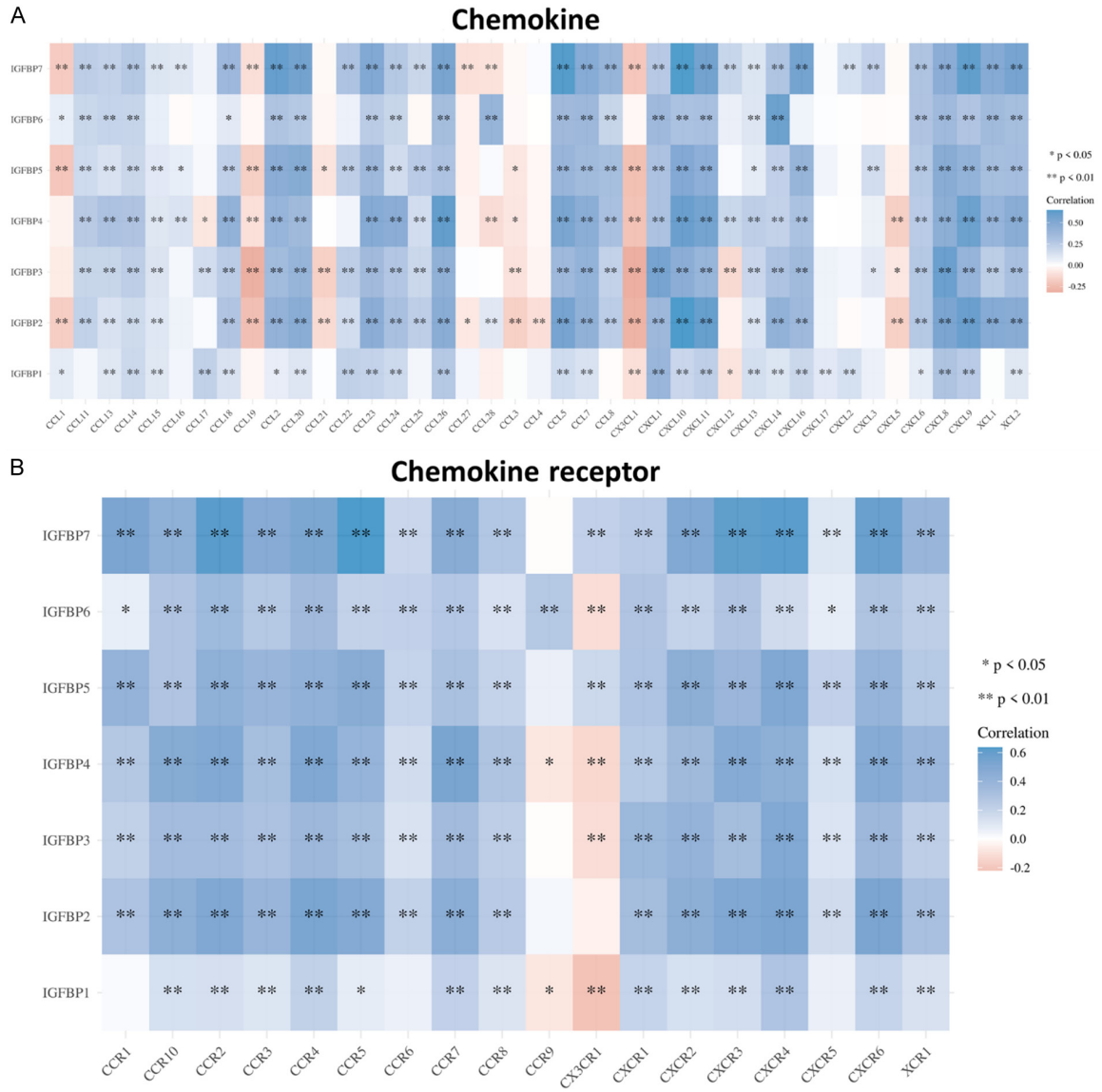
Supplementary Figure 12. Predictive value of IGFBPs for CTRP drug therapy in cancers. The GSCALite was used to evaluate the area under the dose-response curve (AUC) values for drugs and gene expression profiles of IGFBPs in different cancer cell lines. Drug sensitivity and gene expression profiling data of cancer cell lines in CTRP are integrated for investigation. The expression of each gene in the gene set was assessed by Spearman correlation analysis with the small molecule/drug sensitivity (IC50).



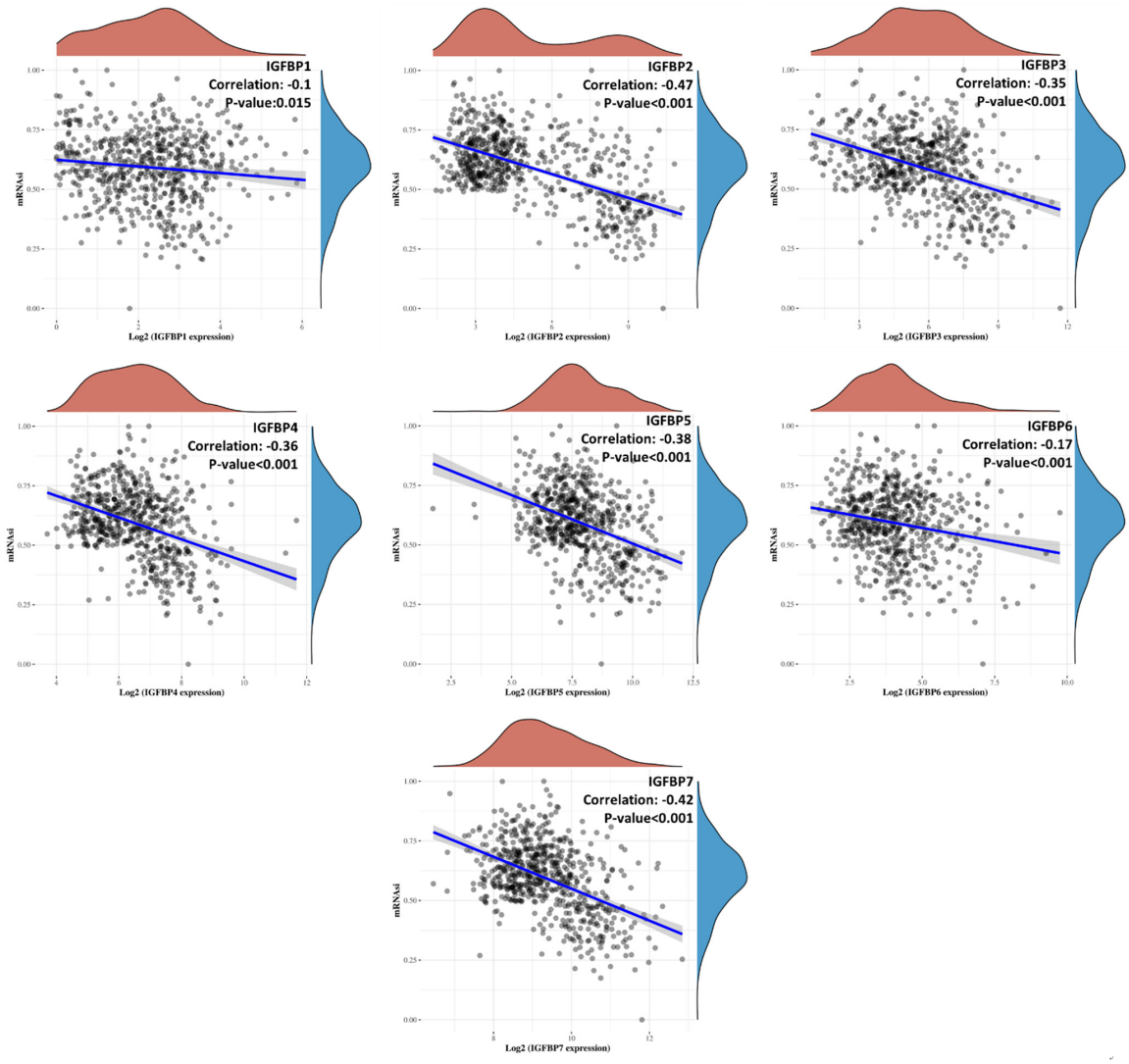
Supplementary Figure 13. Functional prediction of IGFBP mRNA expression and gene interaction network by the GeneMANIA.



Supplementary Figure 14. Correlations between IGFBP expression and functional states in a glioma single-cell dataset. The GSE84465 cohort (n=991) was accessed and analyzed using the CancerSEA. IGFBP1-7 genes were analyzed as a single signature. A. Significant correlations with an |R|>0.2. B. Representative scatter plot of the correlations. Grey points were not considered to compute the correlations. ***P<0.001.



Supplementary Figure 15. Chemokine association of IGFBPs in glioma. TCGA (LGG+GBM) mRNA expression cohort was analyzed. A. Correlations of chemokine expressions and expressions of IGFBPs. B. Correlations of chemokine receptor expressions and expressions of IGFBPs.



Supplementary Figure 16. Correlations of stemness (mRNAsi score) and mRNA expression of IGFBPs. TCGA (LGG+GBM) mRNA expression cohort was analyzed. The OCLR algorithms were used to estimate the stemness.