

Immune-related interaction perturbation networks unravel biological peculiarities and clinical significance of glioblastoma

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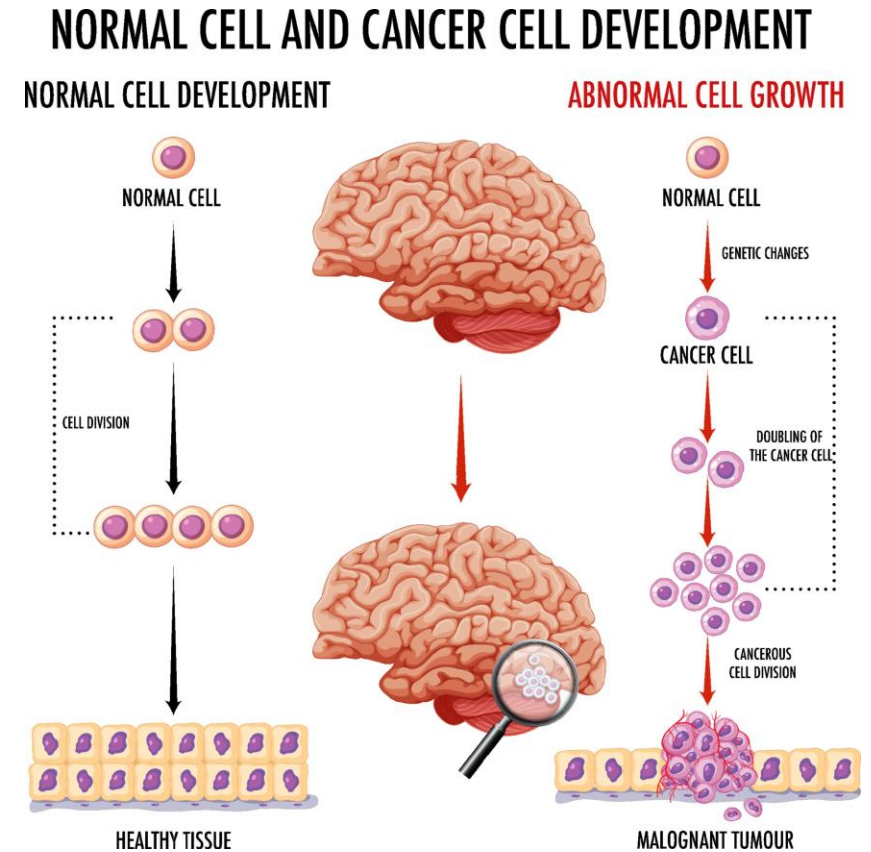
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Introduction

- Glioblastoma (GBM) is endowed with an infiltrative growth pattern and inherent difficulty in treatment, which could be partly attributed to tumor heterogeneity.
- Thus, molecular classification is needed to decipher GBM heterogeneity and facilitate individualized therapies.

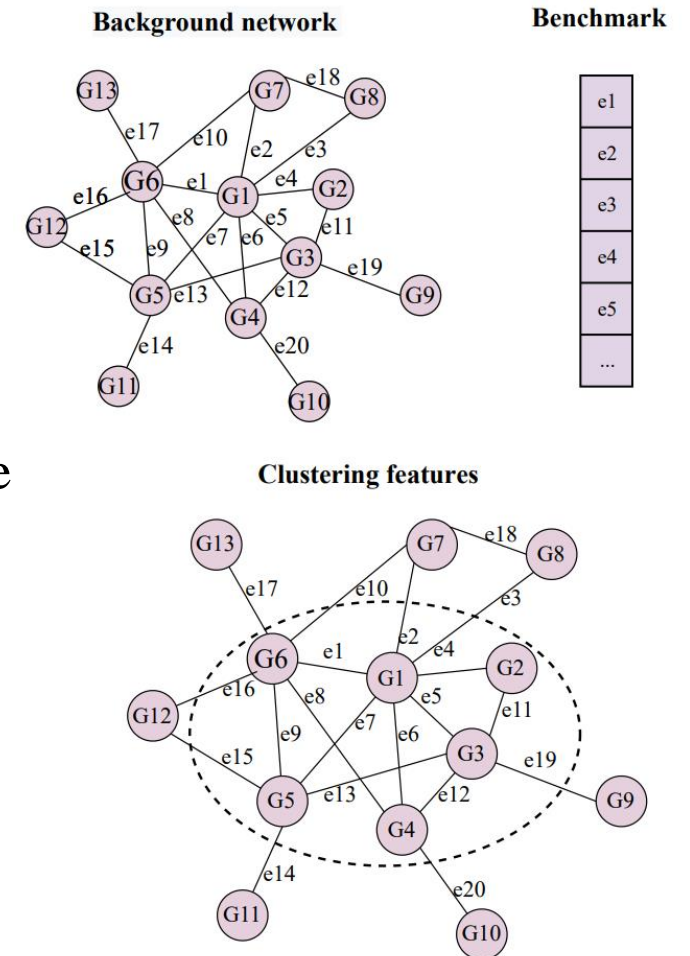


Picture source: <https://www.vecteezy.com/vector-art/6771384-diagram-showing-human-brain-and-cancer>

Introduction

- Previous researches developing subtypes were based on bulk RNA-seq data, which ignored the fact that biological systems are dynamically altered. Conversely, biological networks containing the information of genes and interactions are relatively stable to time and conditions.
- Cancer cells in GBM generated a proangiogenic and inflamed microenvironment, which recruited immune cells and molecules to infiltrate the tumor mass, leading to intricate immune networks in GBM.
- An immune-related interaction-perturbation framework was introduced, which both considered vital interaction information in the biological network and the relationship between immunity and cancer.

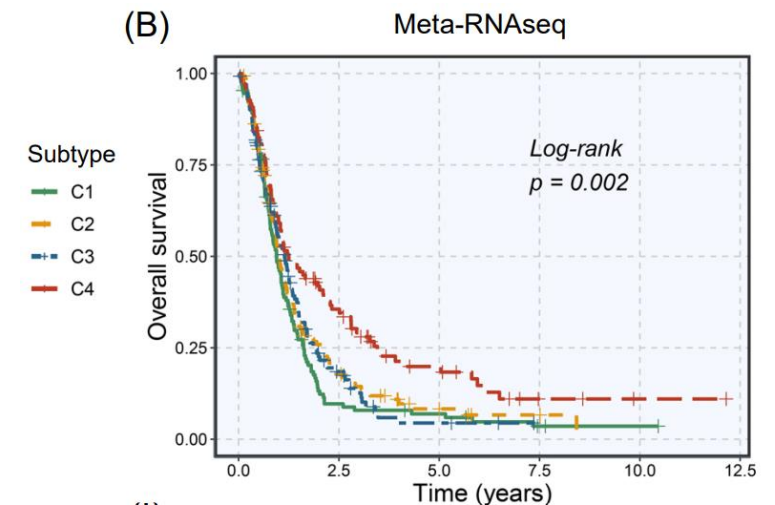
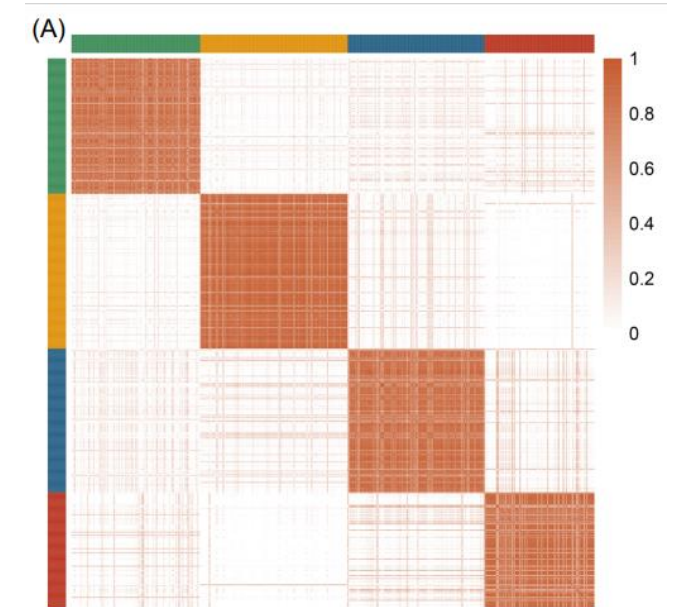
Construction of immune-related interaction perturbation networks



Results

◆ Subtype discovery from the immune-related interaction perturbation matrix

- 1461 interactions (formed by 606 genes) with predominant perturbation in tumor samples and high heterogeneity were retained to perform consensus clustering.
- Based on the interaction-perturbation matrix, 532 GBM samples from the Meta-RNAseq cohort were divided into four groups via consensus clustering.
- Kaplan-Meier survival analysis suggested significant differences in prognosis among four subtypes, in which C4 displayed the most prolonged overall survival (OS) ($p = 0.002$).

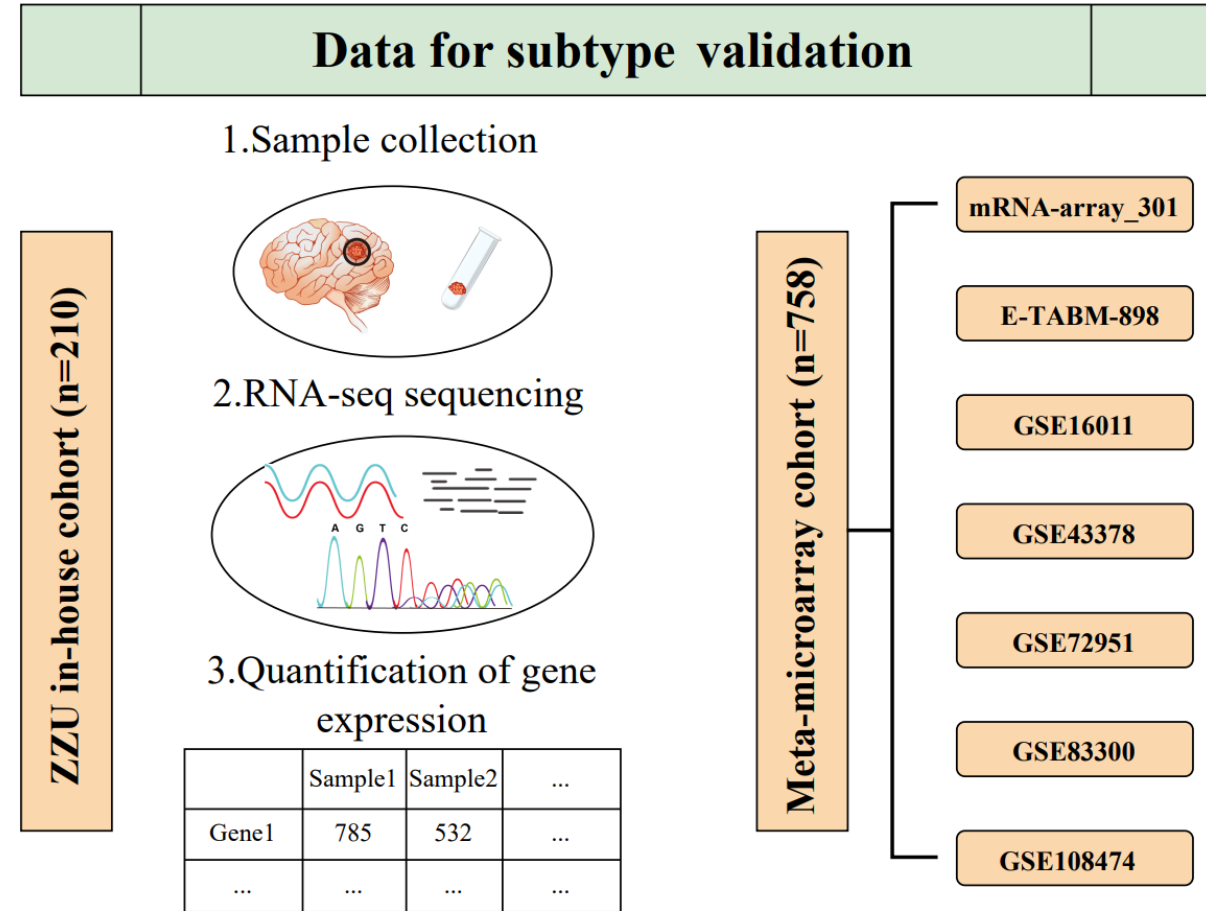


Results

◆ Subtype validation in external and internal cohorts

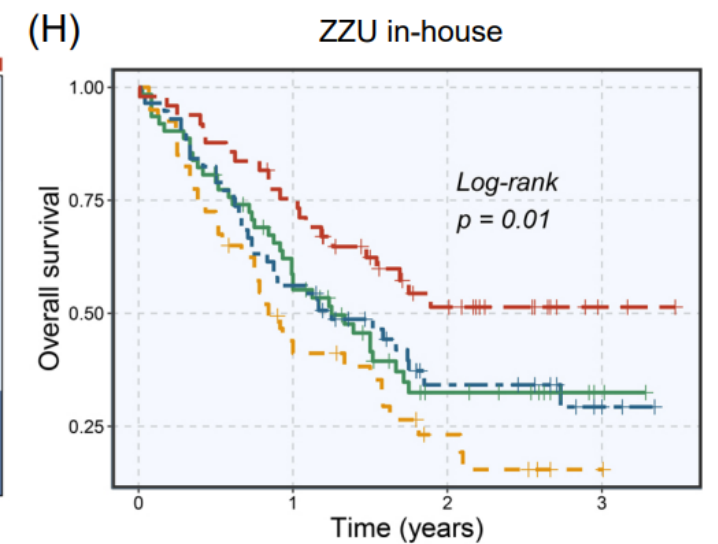
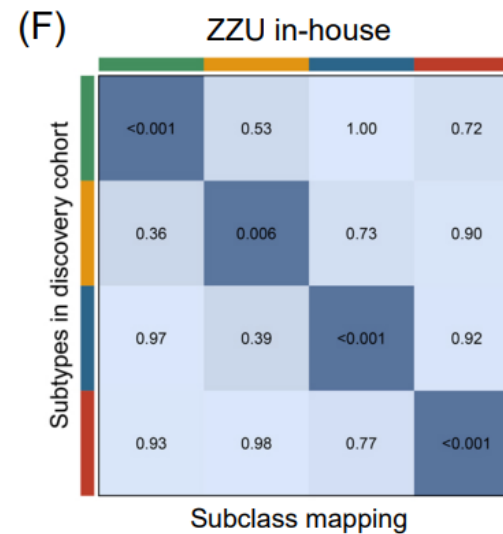
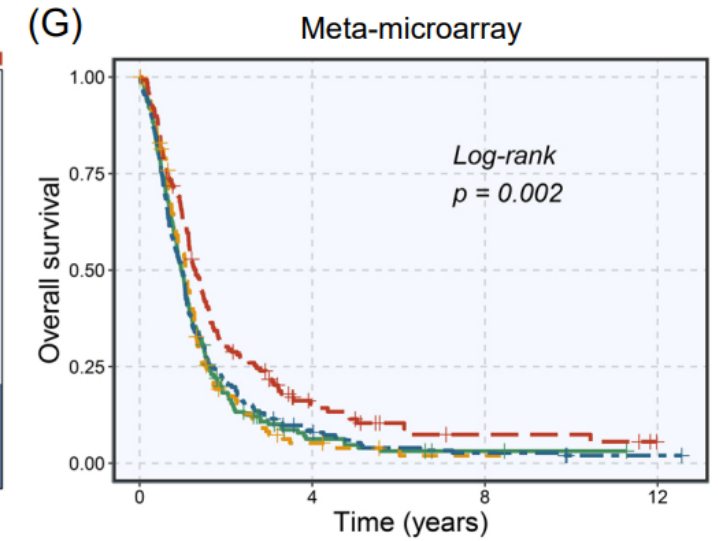
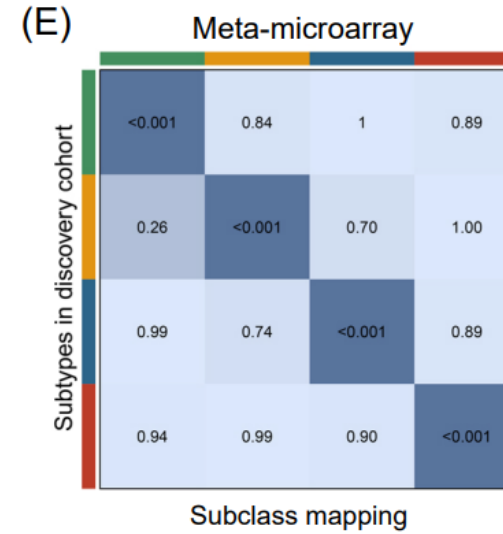
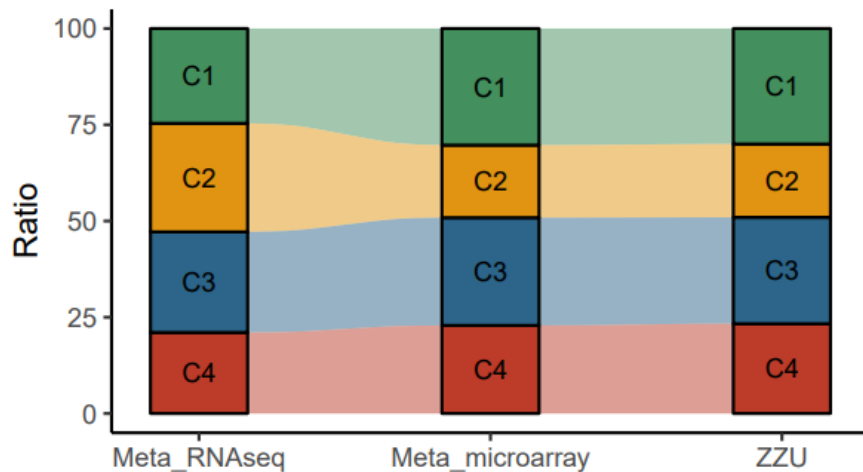
➤ To validate the reliability and reproducibility of our taxonomy in cross-platform cohorts, we conducted nearest template prediction (NTP) in two cohorts:

- **Meta-microarray cohort** (containing 758 eligible GBM samples from public microarray datasets)
- **ZZU in-house cohort** (containing 210 GBM samples from the First Affiliated Hospital of Zhengzhou University [ZZU]).



Results

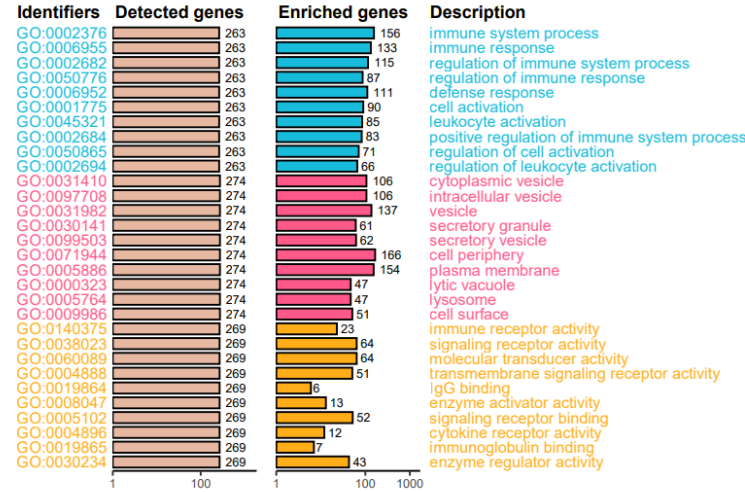
- The two validation cohorts demonstrated similar transcriptome and clinical traits with discovery cohort.
- Four subtypes also maintained comparable proportions across different cohorts.



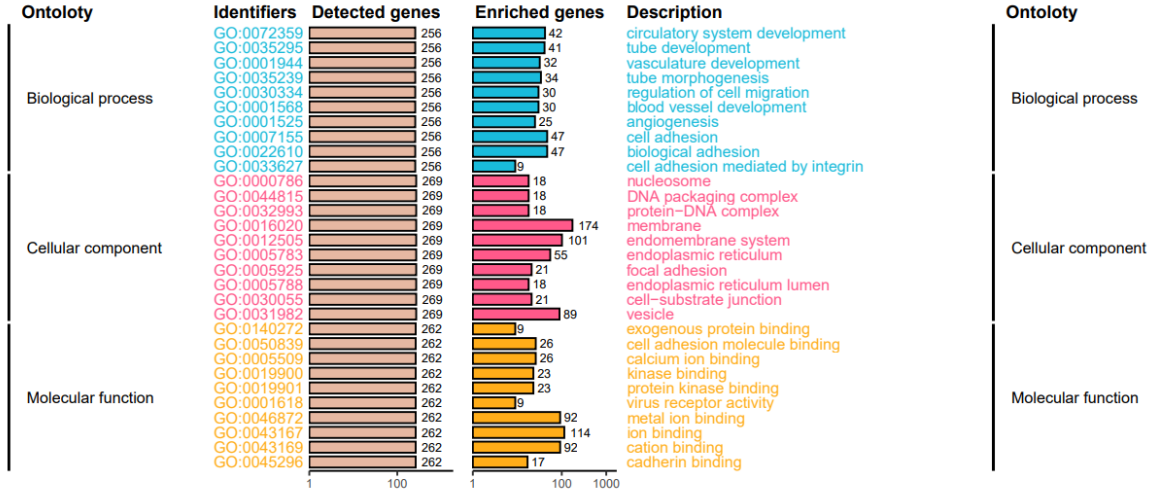
Results

◆ Biological peculiarities underlying four subtypes

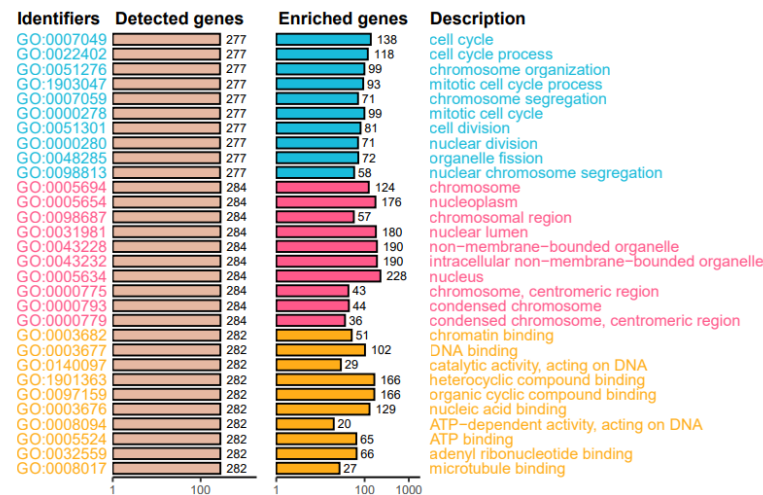
(A) Biological function of C1



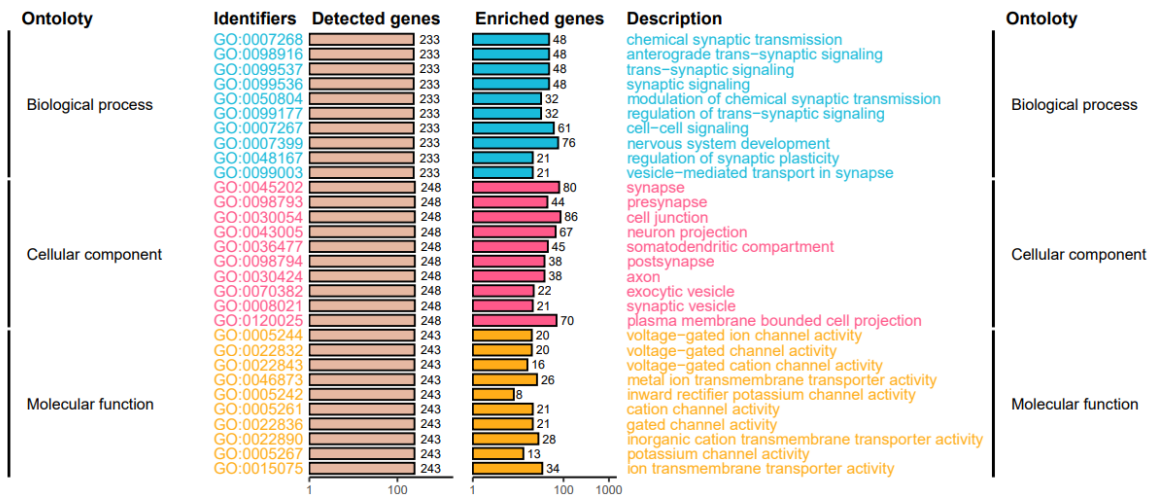
(B) Biological function of C2



(C) Biological function of C3

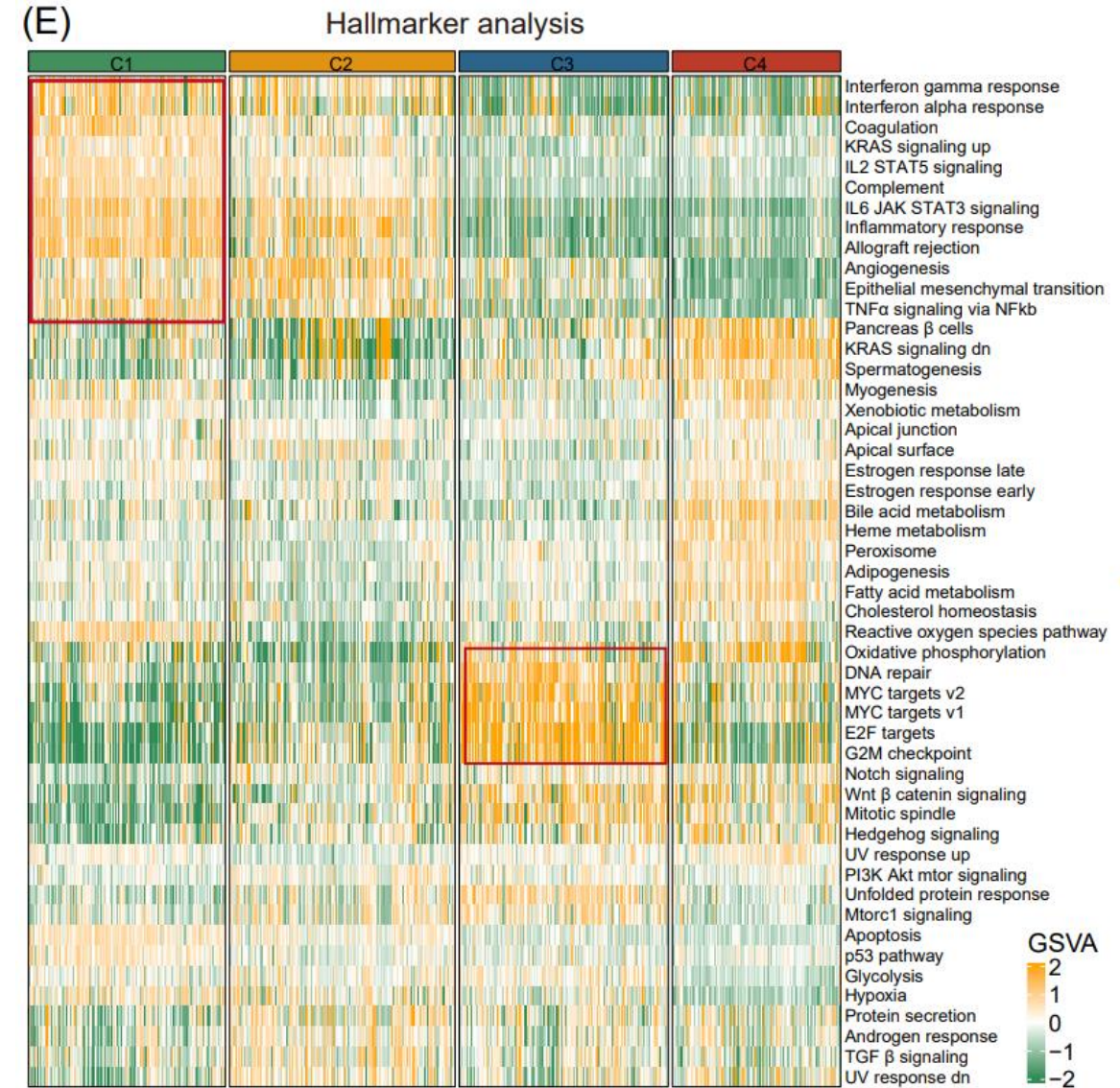
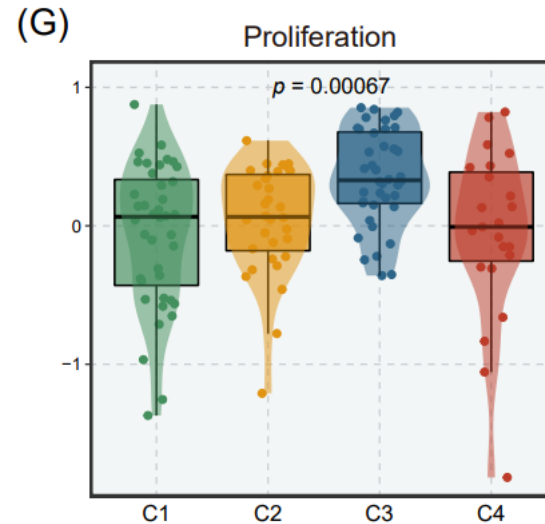
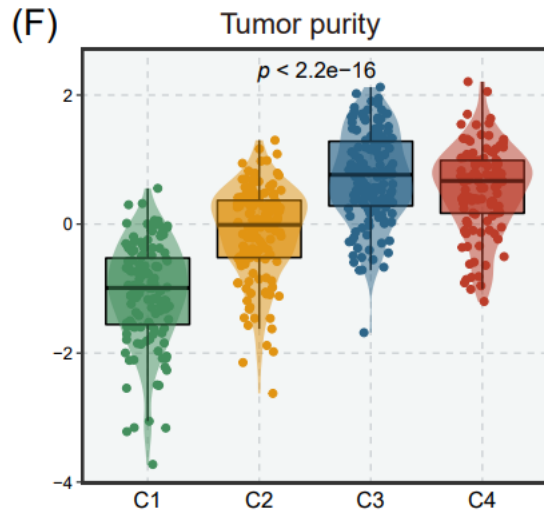


(D) Biological function of C4



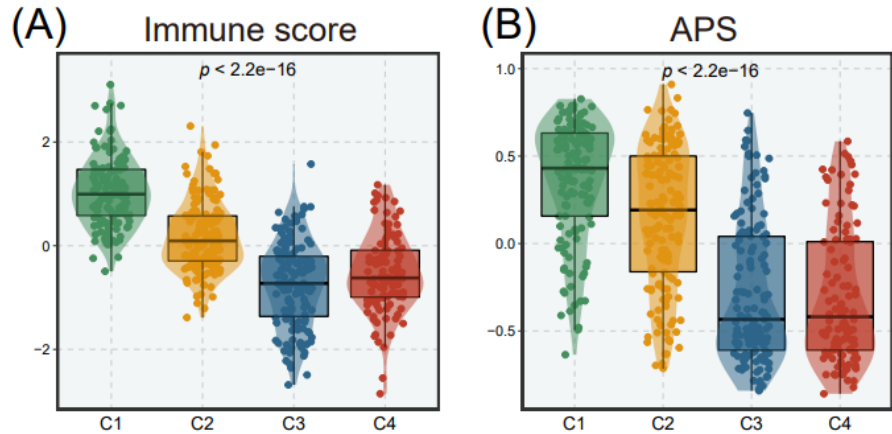
Results

- **C1:** immune-infiltrated GBM
- **C2:** invasive GBM
- **C3:** proliferative GBM
- **C4:** synaptogenesis GBM

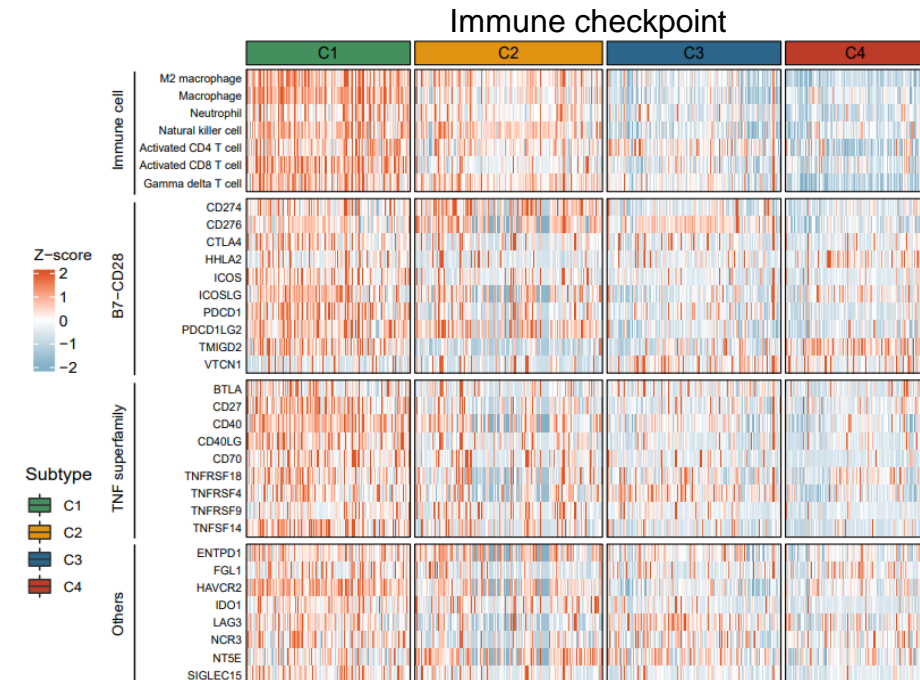
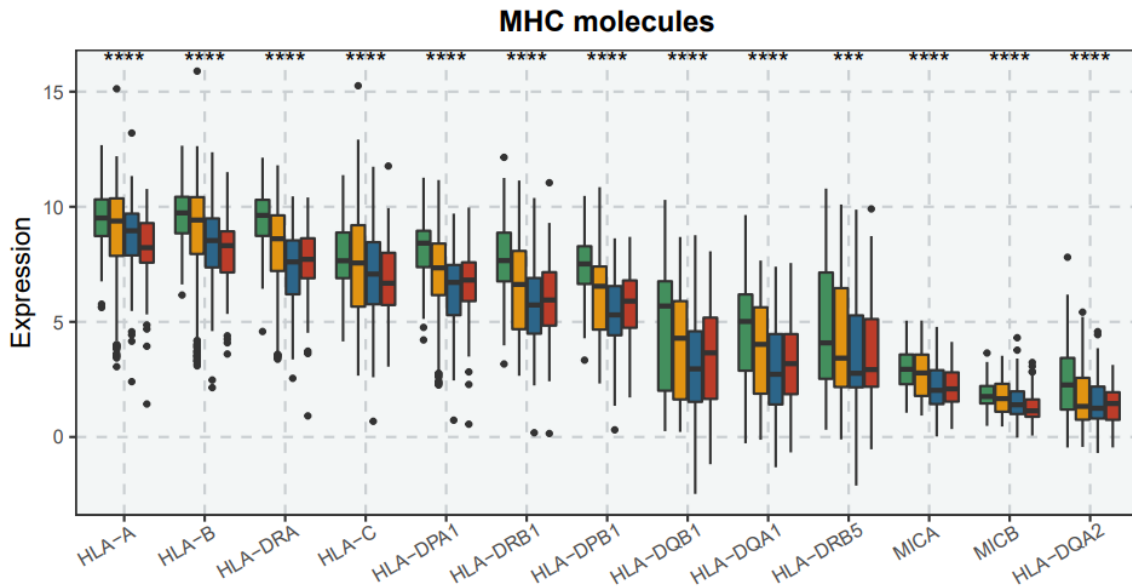


Results

◆ Immune landscape and immunotherapeutic potential of four subtypes



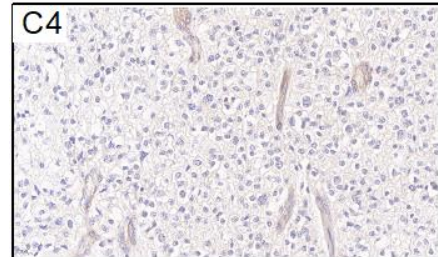
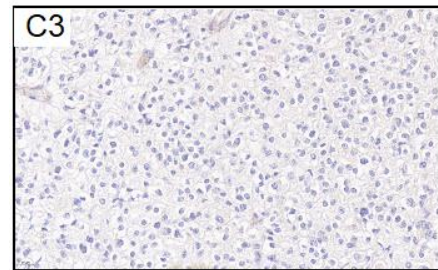
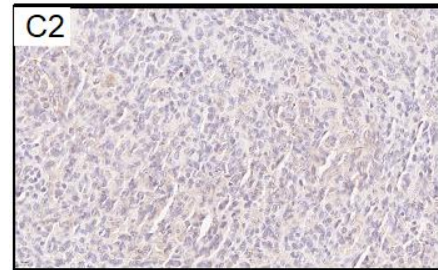
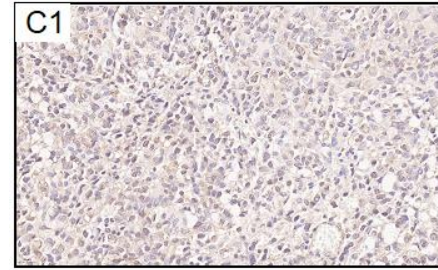
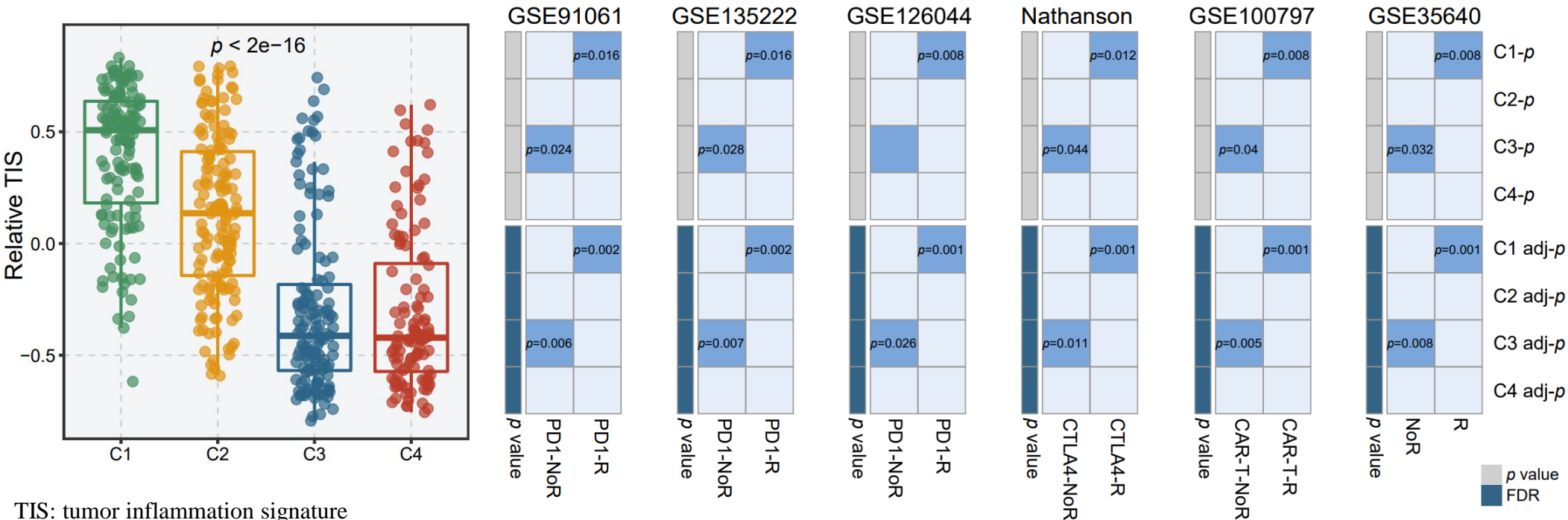
- C1 exhibited a higher immune score and better antigen processing and presenting.
- The expression of immune checkpoint, co-stimulatory and co-inhibitory molecules were also elevated in C1.
- C1 tumors might benefit more from immunotherapy.



MHC: major histocompatibility complex; APS: antigen processing and presenting machinery score

Results

- C1 conveyed the highest TIS score, whereas the lowest score was assigned to C3.
- C1 shared the transcriptional traits with responders from all immunotherapy cohorts. Oppositely, C3 demonstrated analogical expression patterns with non-responders.
- C1 demonstrated a notably elevated level of PD-L1 expression, whereas C3 exhibited a comparatively inferior level.

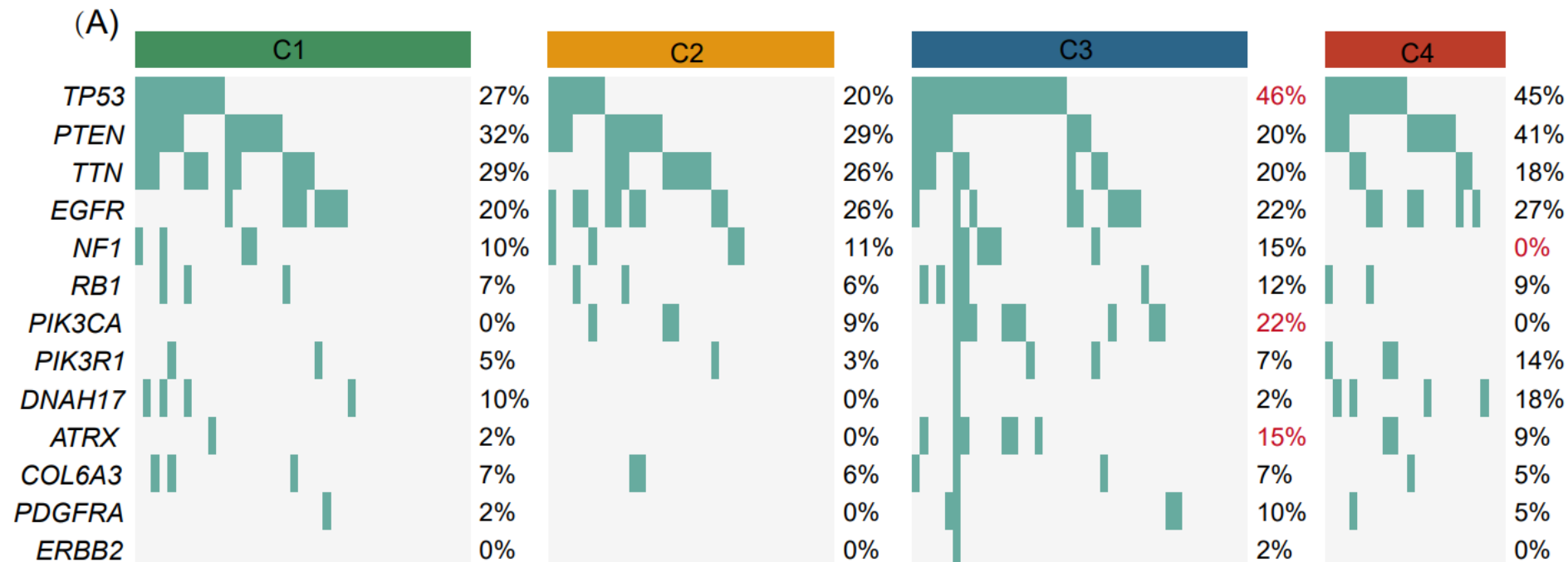


■ p value
■ FDR

Results

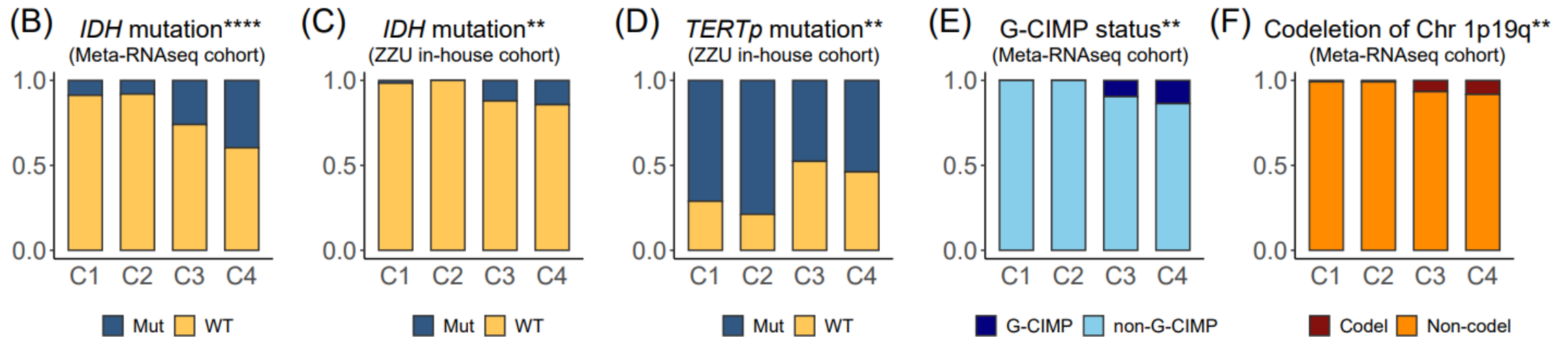
◆ Four subtypes conveyed distinct genomic features

- *TP53*, *ATRX*, and *PIK3CA* mutations were prevalent in C3, which was consistent with the proliferative peculiarity of C3.
- *NF1* mutations, which were regarded as a biomarker for treatment-resistant gliomas, demonstrating scarce frequency in C4.



Results

- *TERTp* mutations, the independent indicator of poor clinical outcome, were enriched in C2.
- C4 was endowed with the highest *IDH* mutations, corresponding to the favorable prognosis of C4.
- G-CIMP status and codeletion of chr1p19q status were particularly evident in C4, which were both favorable factors for prognosis, further validating the best clinical outcome of C4.



Results

◆ Potential therapy agents in four subtypes

- We detected subtypes-specific interventions for four subtypes, which also concordant with their respective peculiarities.

Drugs	Specific	Scaled IC50 (mRNA)				Action	Clinical stage	Putative targets	Targeted pathways
		C1	C2	C3	C4				
AZD6482	C1	-0.39	-0.19	0.54	0.04	Targeted	in clinical development	PI3Kbeta	PI3K signaling
Vinblastine	C2	0.09	-0.24	0.08	0.12	Cytotoxic	clinically approved	Microtubules	Cytoskeleton
Axitinib	C2	-0.05	-0.49	0.47	0.14	Targeted	in clinical development	PDGFR, KIT, VEGFR	RTK signaling
Masitinib	C2	0.34	-0.34	-0.00	0.07	Targeted	clinically approved	KIT	RTK signaling
OSI-930	C2	0.01	-0.26	0.13	0.18	Targeted	in clinical development	KIT, VEGFR, PDGFR	RTK signaling
Pazopanib	C2	0.30	-0.51	0.17	0.12	Targeted	in clinical development	VEGFR, PDGFRA, PDGFRB, KIT	RTK signaling
Bryostatins1	C2	0.22	-0.57	-0.27	0.84	Targeted	in clinical development	PRKC	Other
Vorinostat	C3	0.23	0.33	-0.48	-0.12	Targeted	clinically approved	HDAC inhibitor Class I, IIa, IIb, IV	Chromatin histone acetylation
Cisplatin	C3	0.39	0.31	-0.58	-0.14	Cytotoxic	clinically approved	DNA crosslinker	DNA replication
Cytarabine	C3	0.10	0.50	-0.44	-0.24	Cytotoxic	clinically approved	DNA synthesis	DNA replication
Temozolomide	C3	0.50	0.36	-0.67	-0.24	Cytotoxic	clinically approved	DNA alkylating agent	DNA replication
AZD7762	C3	-0.13	0.59	-0.35	-0.20	Targeted	in clinical development	CHEK1, CHEK2	Genome integrity
MK-2206	C3	0.29	0.46	-0.58	-0.24	Targeted	in clinical development	AKT1, AKT2	PI3K signaling
Midostaurin	C3	0.45	0.28	-0.56	-0.21	Targeted	in clinical development	KIT	RTK signaling
Bicalutamide	C3	0.33	0.26	-0.51	-0.10	Targeted	clinically approved	ANDR (androgen receptor)	Other
Ruxolitinib	C3	0.42	0.49	-0.64	-0.36	Targeted	clinically approved	JAK1, JAK2, TYK2	Other
Tamoxifen	C3	0.12	0.63	-0.52	-0.33	Targeted	clinically approved	ER	Other
Nilotinib	C4	0.09	0.27	0.05	-0.53	Targeted	clinically approved	ABL	ABL signaling
Embelin	C4	0.12	0.70	-0.42	-0.56	Targeted	in clinical development	XIAP	Apoptosis regulation
AT-7519	C4	0.02	0.07	0.16	-0.31	Targeted	in clinical development	CDK9	Cell cycle
Vinorelbine	C4	-0.01	0.67	-0.25	-0.58	Cytotoxic	clinically approved	Microtubules	Cytoskeleton
5-Fluorouracil	C4	0.35	0.40	-0.18	-0.72	Cytotoxic	clinically approved	DNA antimetabolite	DNA replication
Bleomycin	C4	0.36	0.63	-0.38	-0.80	Cytotoxic	clinically approved	DNA damage	DNA replication
Doxorubicin	C4	0.46	0.58	-0.50	-0.70	Cytotoxic	clinically approved	DNA intercalating	DNA replication
Cetuximab	C4	0.35	0.50	-0.28	-0.73	Targeted	clinically approved	EGFR	EGFR signaling
TAK-715	C4	0.42	0.65	-0.51	-0.73	Targeted	in clinical development	p38a	JNK and p38 signaling
ZSTK474	C4	-0.17	0.69	-0.19	-0.49	Targeted	in clinical development	PI3K	PI3K signaling
OSI-027	C4	0.11	0.78	-0.15	-0.99	Targeted	in clinical development	MTORC1/2	TOR signaling
Bexarotene	C4	0.05	0.64	-0.22	-0.64	Targeted	clinically approved	Retinoic acid X family agonist	Other
Shikonin	C4	0.06	0.84	-0.36	-0.75	Not defined	in clinical development	unknown	Other
Tipifarnib	C4	0.27	0.61	-0.34	-0.71	Targeted	in clinical development	Farnesyl-transferase (FNTA)	Other

Summary

- An immune-related interaction-perturbation framework was introduced, which both considered vital interaction information in the biological network and the relationship between immunity and cancer.
- Four glioblastoma subtypes endowed with distinct clinical outcomes and biological features were identified and validated based on the immune-related interaction-perturbation network.
- This taxonomy might be a promising platform to decipher the heterogeneity of glioblastoma and facilitate tailored management.

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