

# Multi Omics Profiling and Clustering Low Grade Glioma Based on Integrated Stress Status

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## Primary research

**Keywords:** Glioma, integrated stress response, immune microenvironments

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# Abstract

**Background:** Although the prognosis of low-grade glioma (LGG) is better than that of glioblastoma (GBM), there are still some patients who will develop into high-grade glioma. Integrated stress response contributed to the malignant transformation of tumor. As there is few research focus on the integrated stress status in LGG, it is urgent to profile and re-classify LGG based on integrated stress response (ISR).

**Methods:** Glioma patients were obtained from the Chinese Glioma Genome Atlas ( the Cancer Genome Atlas (TCGA) and GSE16011 cohorts. Statistical 8 analyses were conducted by GraphPad Prism and R language.

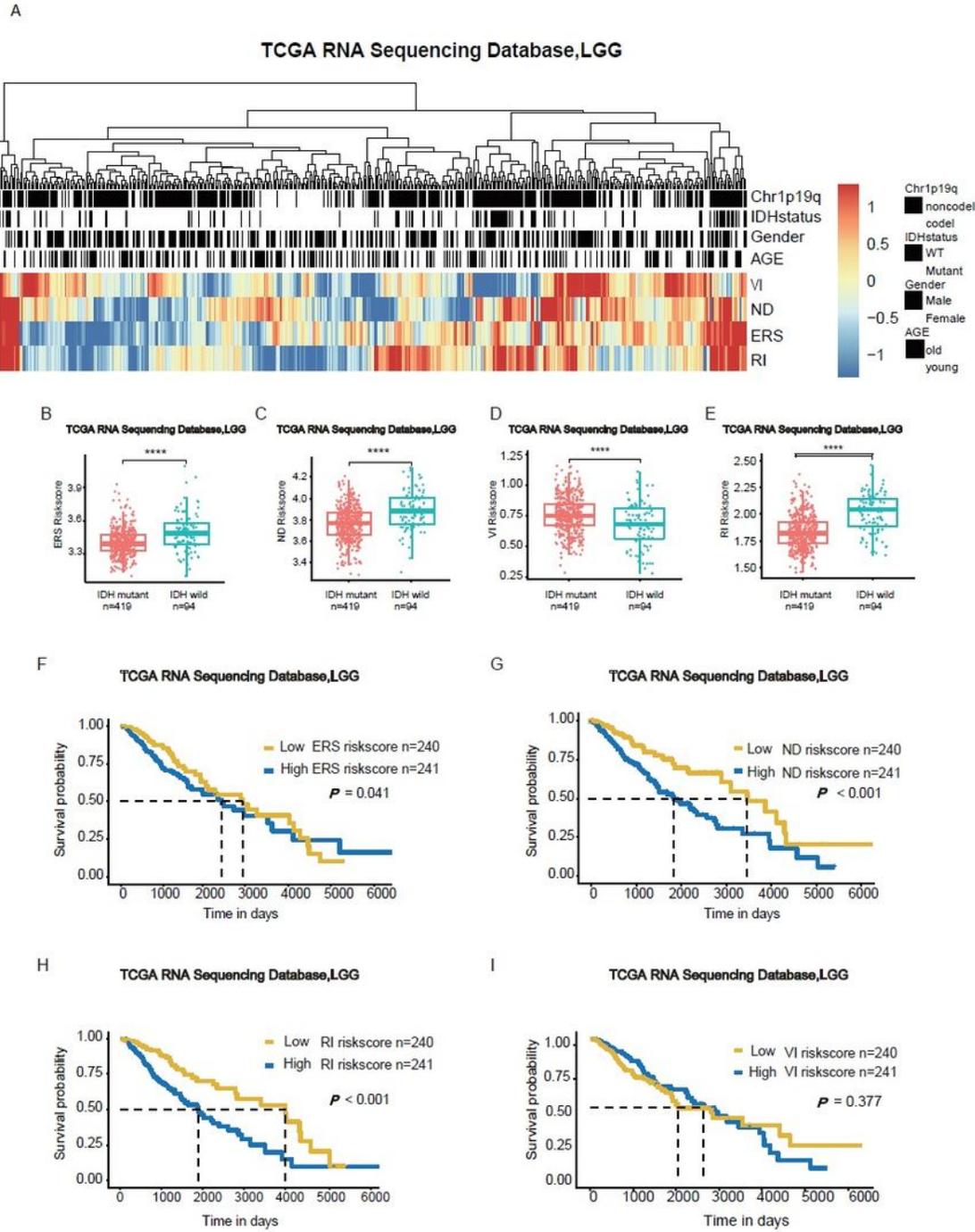
**Results:** We quantified four types of integrated stress response respectively. The relationship between the four stress states and the clinical characteristics of LGG was analyzed. Then we re-classified the patients based on these four scores, we found that cluster 1 had the worst prognosis, whereby cluster 3 had the best prognosis. We also established an accurate ISR risk signature to predicting cluster 1. We found that immune response and suppressive immune cell components were more enriched in the high-risk group. We also profiled the genomic difference between low and high risk groups, including the non-missense mutation of driver genes and the condition of copy number variation (CNV).

**Conclusion:** LGG patients could be divided into four clusters based on the integrated stress status, cluster 1 exhibited malignant transformation trends. ISR signature could reflect the traits of cluster 1 well, high ISR score indicated worse prognosis and enriched inhibitory immune microenvironments.

## Full Text

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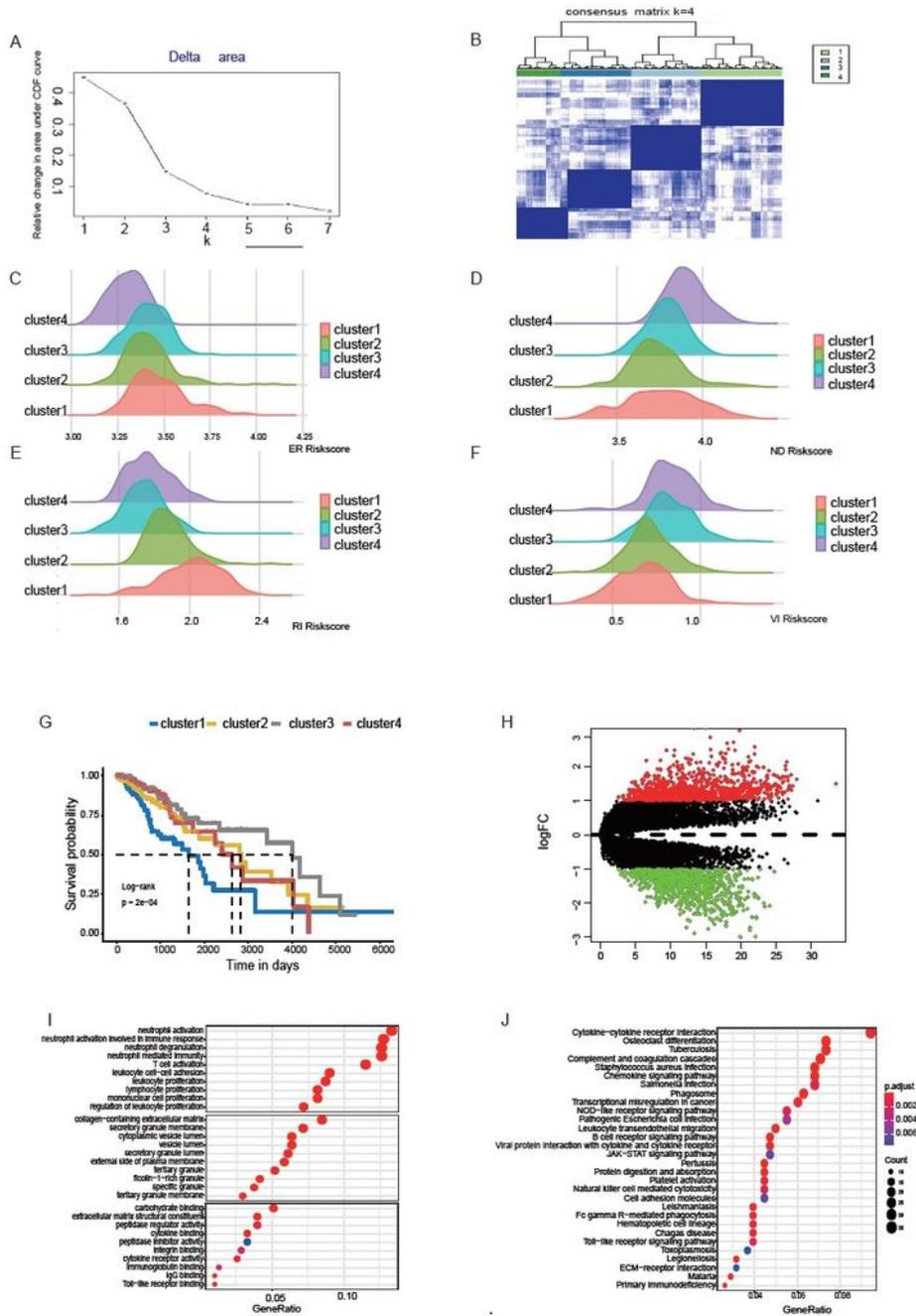
## Figures



**Figure 1**

Estimating the clinical value of four ISR related scores in LGG. (A): The expression pattern of the four stresses response related score with other clinical characteristics of LGG. (B-E) High risk score patients of ERS, ND, RI were specifically enriched in the IDH1 wild type while low risk score patients of VI were specifically enriched in the IDH1 wild type in LGG. (F-H) High risk score group of ERS, ND, RI exhibited an unfavorable prognosis in LGG of TCGA RNA sequencing cohorts. (I) No prognostic significance of VI risk

score in LGG of TCGA RNA sequencing cohorts. Notes: \*\*\*\* means  $P < 0.0001$ , ERS means endoplasmic reticulum stress, ND means nutrient deprivation, RI means redox imbalance, VI mean Viral infection.



**Figure 2**

Re-clustering and profiling LGG patients based on these four ISR related scores. (A-B) Unsupervised clustering of LGG based on four ISR related scores by using k-means method; C-F The distributed patterns of these four ISR related scores among four clusters; (G) Overall survival analyses among the four cluster

samples. (H) Volcano map of the differentially expressed genes between the cluster 3 and cluster 1 subtypes; (I) GO enrichment of the differentially expressed genes between the cluster 3 and cluster 1 subtypes; (J) KEGG enrichment of the differentially expressed genes between the cluster 3 and cluster 1 subtypes. Notes: ISR means integrated stress response. OS means overall survival

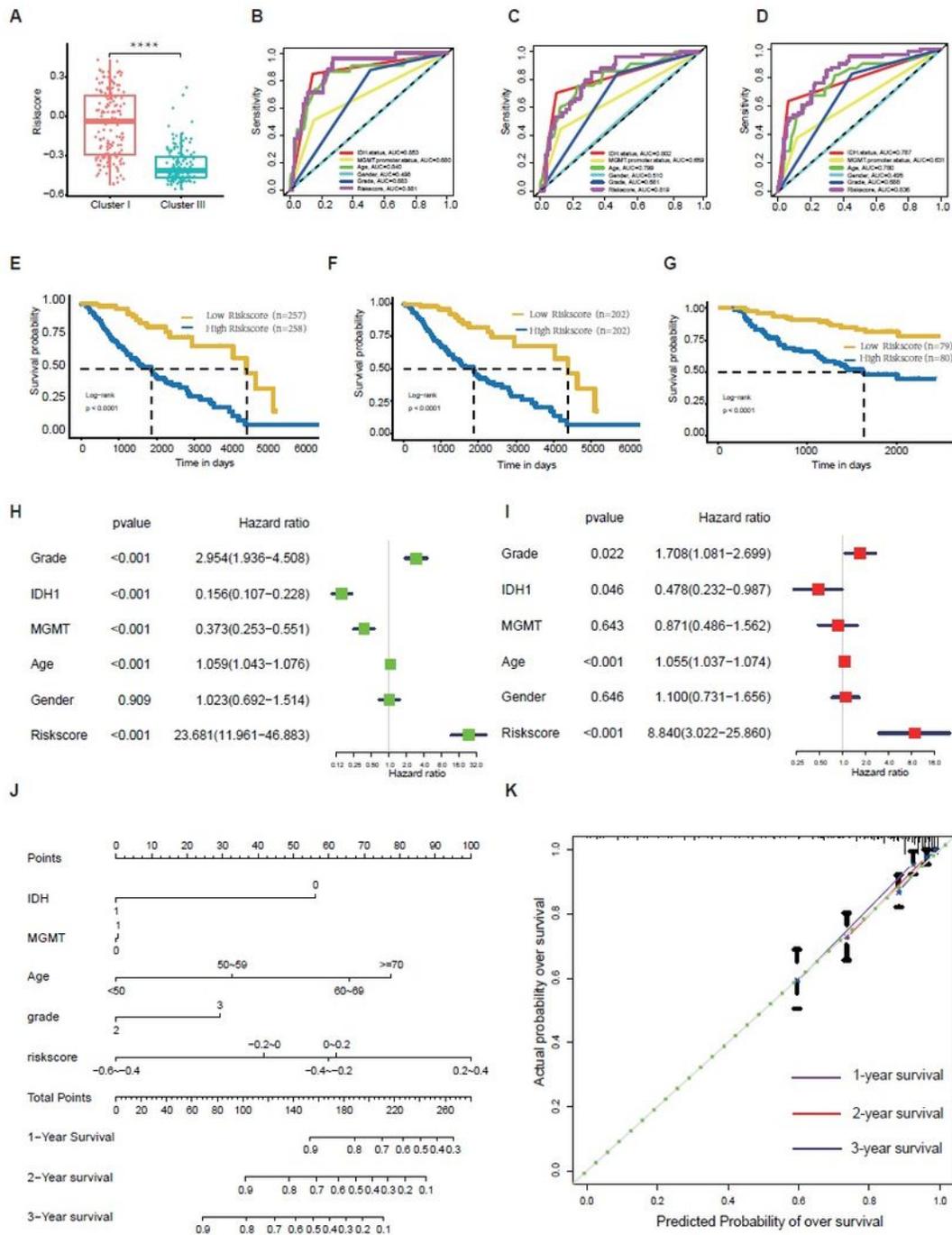
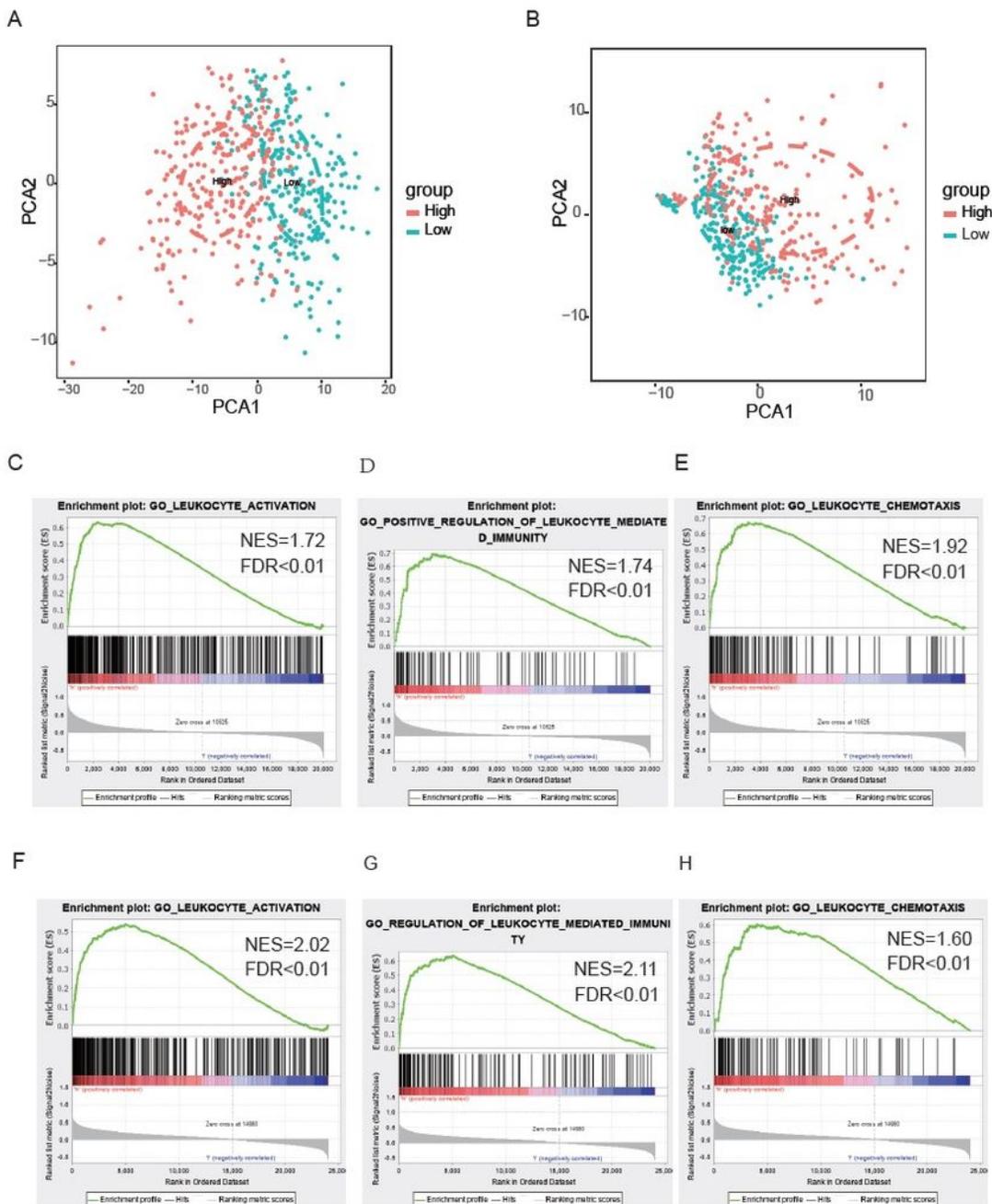


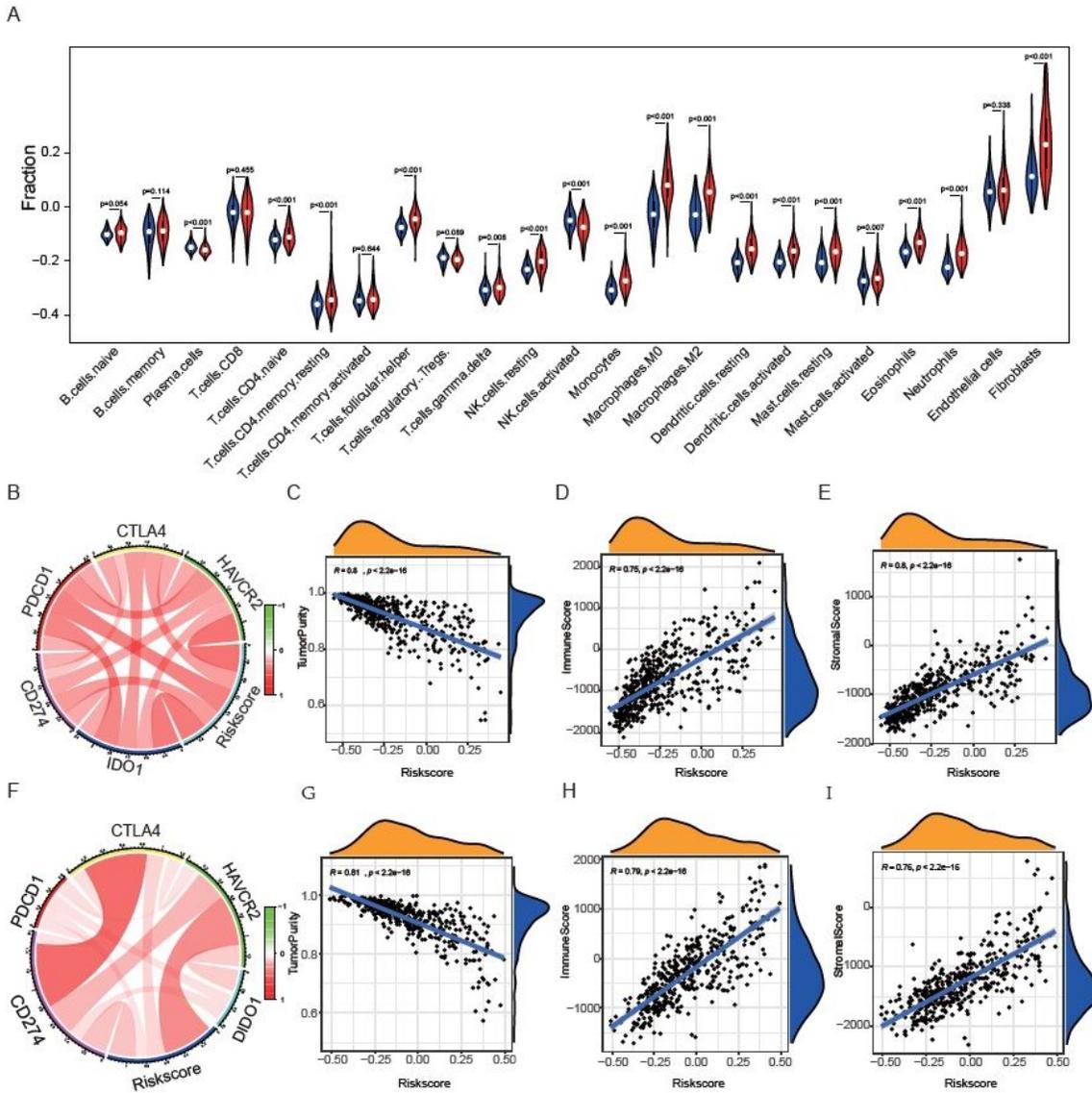
Figure 3

Cluster 1 related ISR risk signature is an independent prognostic factor in LGG cohort. (A) Cluster 1 and cluster 3 exhibited extremely different risk score. (B-D) ROC curves of the risk score to predict 1 year, 2 years, and 3 years of survival in TCGA cohort. (E) The high risk group exhibited a striking shorter survival times in LGG of TCGA RNA-sequencing cohorts. (F-G) In the other two validation cohorts, there was also an unfavorable prognosis in the high-risk group. (H-I): Univariate and multivariate cox analyses of several clinical parameters in the LGG patients. (J-K): Nomogram and the calibration plot of the combined model including the ISR risk signature and other important clinical factors.



**Figure 4**

Different immune statuses between the high and low risk groups. (A-B) PCA showed that the LGG patients in the high and low-risk groups were distributed in different immune statuses; (C-H): GSEA suggested that leukocyte related processes were enriched in the high risk group of the TCGA and CGGA RNA sequencing cohorts.



**Figure 5**

Corresponding relationship between ISR risk score and immune microenvironment. (A) The quantified score of immune gene set showed that patients with high risk score of integrated stress was highly

infiltrated with macrophages of TCGA cohort; (B, F) ISR risk score correlated 1 with immunosuppressive checkpoints in the TCGA and CGGA sequencing cohort.; (C, G) IRS risk 2 score showed a negative correlation with tumor purity in the TCGA and CGGA RNA sequencing 3 cohorts; (D, E, H, I) IRS risk score showed a positive correlation with stromal score and immune 4 score in the TCGA and CGGA RNA sequencing cohorts.

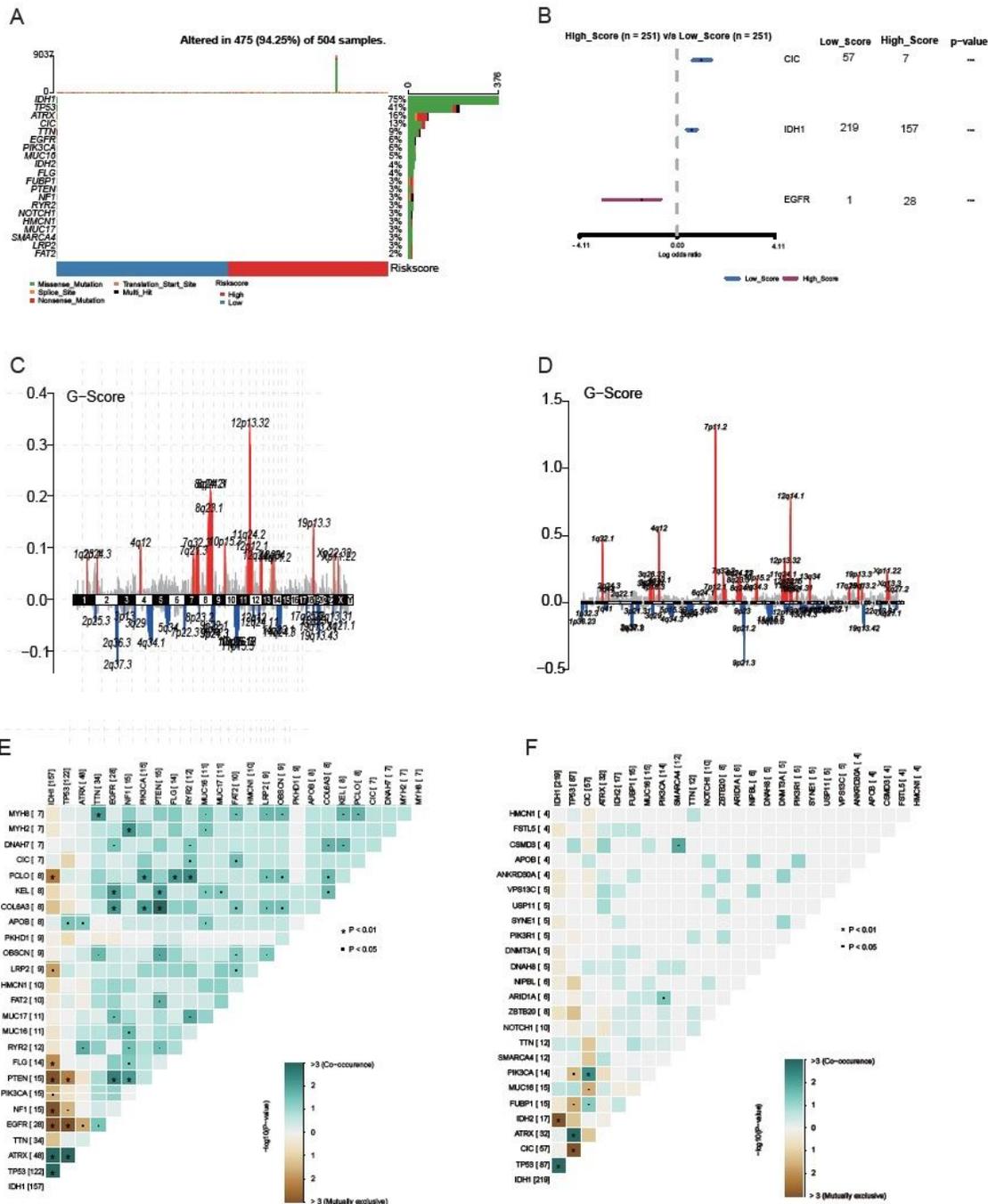


Figure 6

Specific somatic mutations and copy number changes between high and low ISR risk score groups. (A) Low and high ISR risk score groups mutation information illustrated in the somatic mutation spectrum. (B) Various mutated genes between high and low ISR risk score groups. (C, D) Copy number variation (CNV) based on low and high ISR risk score levels. (E, F) Correlation analyses of mutated genes in high and low risk groups in the TCGA RNA sequencing cohorts.

## Supplementary Files

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