

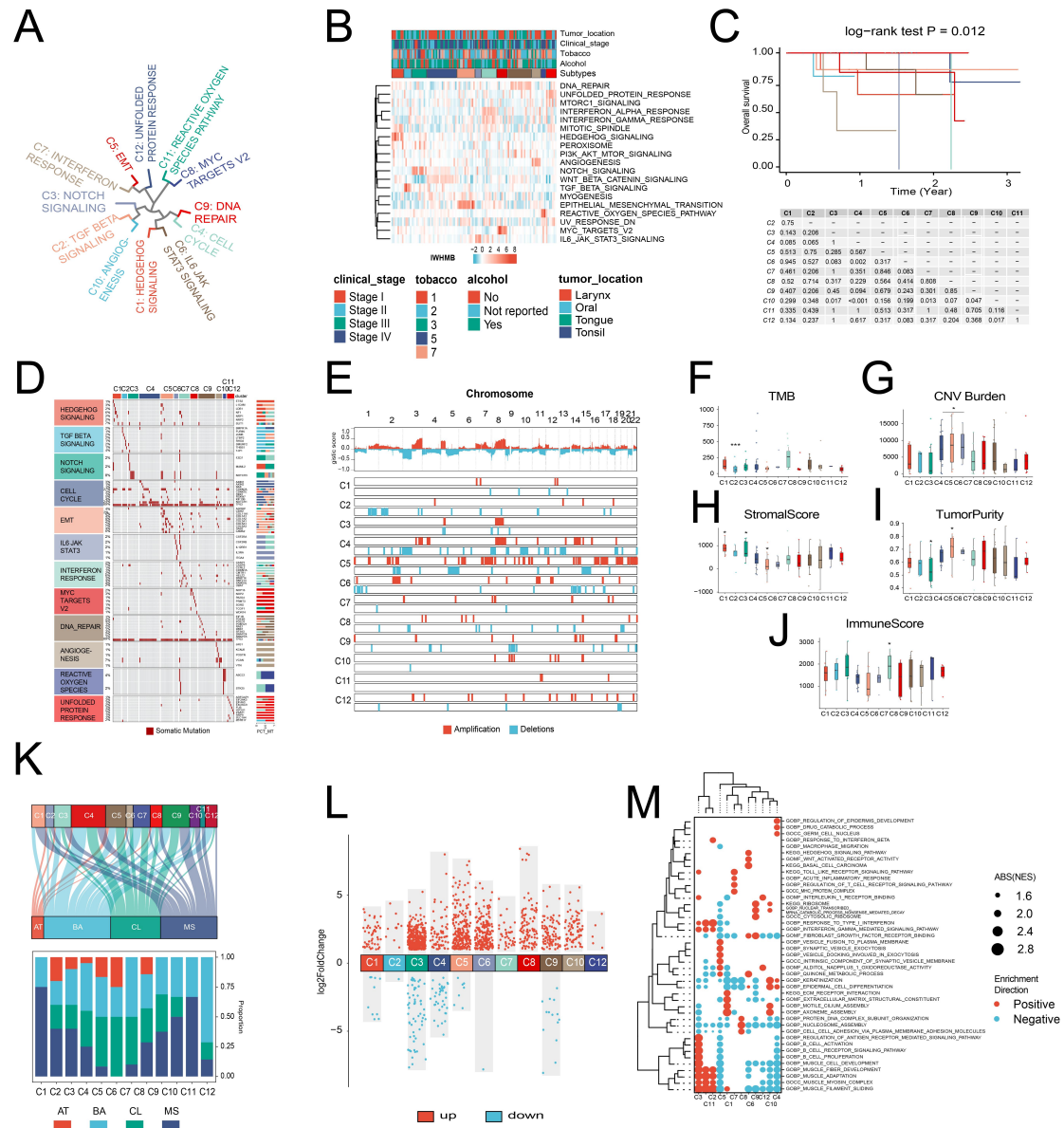


Fig. S1. Multiomics differences in IWHMB-associated cancer subtypes in Chen, H et al. 2021 cohort. **(A)** Circular cluster dendrogram showing 12 IWHMB-associated cancer subtypes. **(B)** Heatmap showing 12 IWHMB-associated cancer subtypes. **(C)** Clinical prognosis of 12 IWHMB-associated cancer sub-types. **(D)** Somatic mutation waterfall plot of 12 IWHMB-associated cancer subtypes. **(E)** Differential copy number changes (Fisher's precision probability test pvalue<0.05) in 12 IWHMB-associated cancer subtypes. **(F)** TMB of 12 IWHMB-associated cancer subtypes. **(G)** CNV Burden of 12 IWHMB-associated cancer subtypes. **(H-J)** StromalScore, TumorPurity and ImmuneScore of 12 IWHMB-associated cancer subtypes. **(K)** Relationship between IWHMB-associated cancer subtypes and Kech subtypes. **(L)** DEGs of 12 IWHMB-associated cancer subtypes. **(M)** GSEA pathway enrichment of 12

IWHMB-associated cancer subtypes.

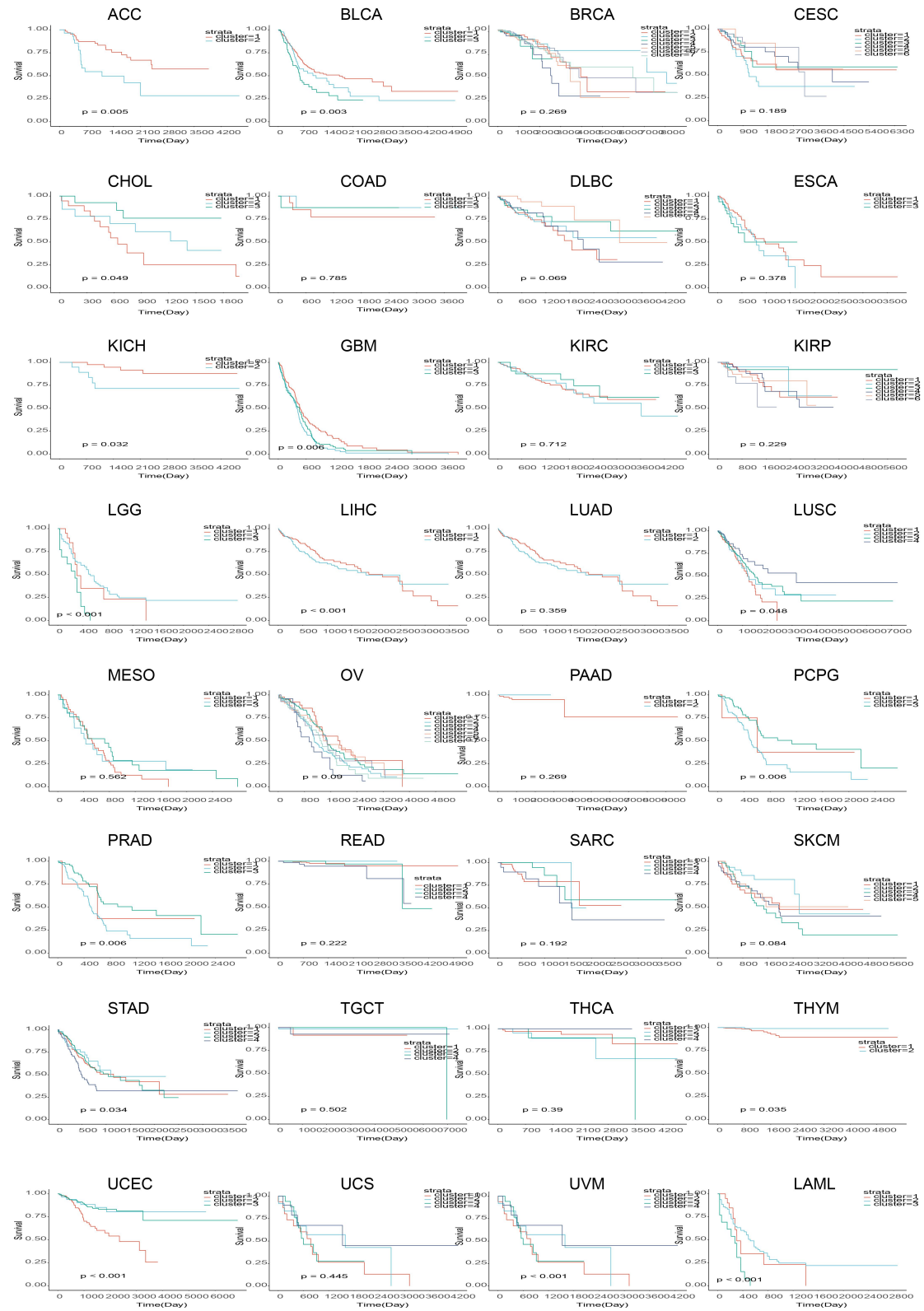


Fig. S2. Relationship between IWHMB-related subtypes and clinical prognosis in 32 TCGA cancers.

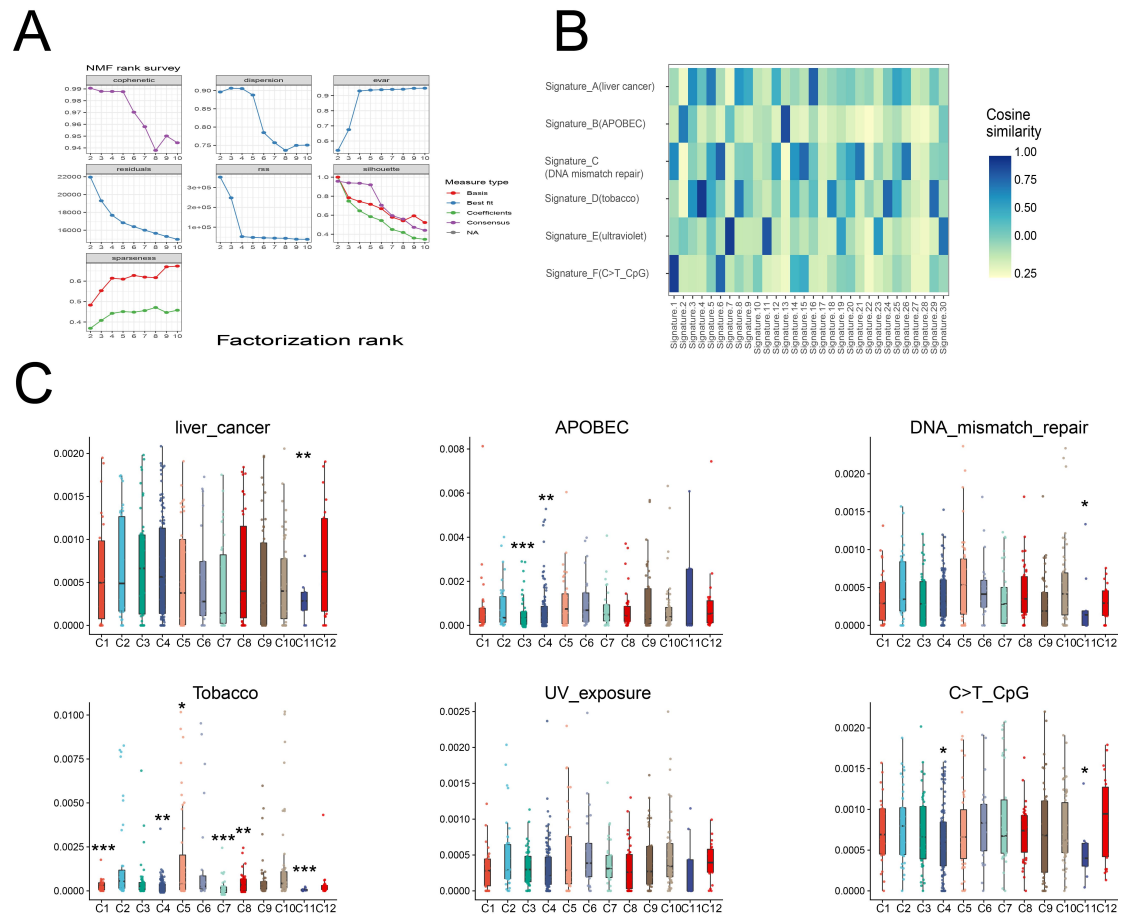


Fig. S3. Mutation Signatures in TCGA HNSCC cohort. **(A)** NMF of mutation signatures in the TCGA HNSCC cohort. **(B)** Cosine similarity of mutation signatures in the TCGA HNSCC cohort with annotated signatures recorded in the COSMIC database. **(C)** Association of 6 mutational signatures with IWHMB-related subtypes in the TCGA HNSCC cohort.

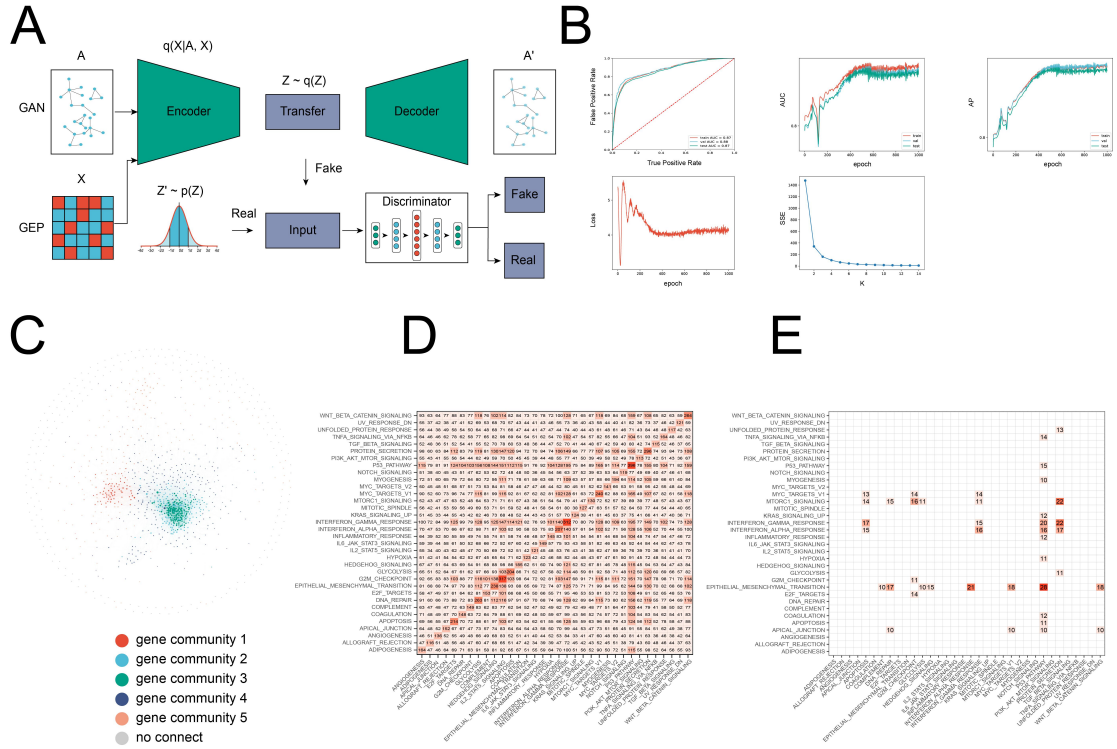


Fig. S4. ARGVA algorithm is used to identify Communities of IRG. **(A)** Schematic diagram of ARGVA algorithm. **(B)** Iteration period and loss function of ARGVA algorithm. **(C)** Communities visualization. **(D)** Interaction plot of 50 HGS disturbed genes. **(E)** Interaction plot of 50 HGS disturbed genes with the HGS itself.

cohorts. **(D)** Network similarity of Communities in multiple HNSCC cohorts. **(E)** Community 1 network visualization. Different colors represent that gene is interfered by different IWHMB of HGS. **(F)** Enriched path visualization in Community 1.

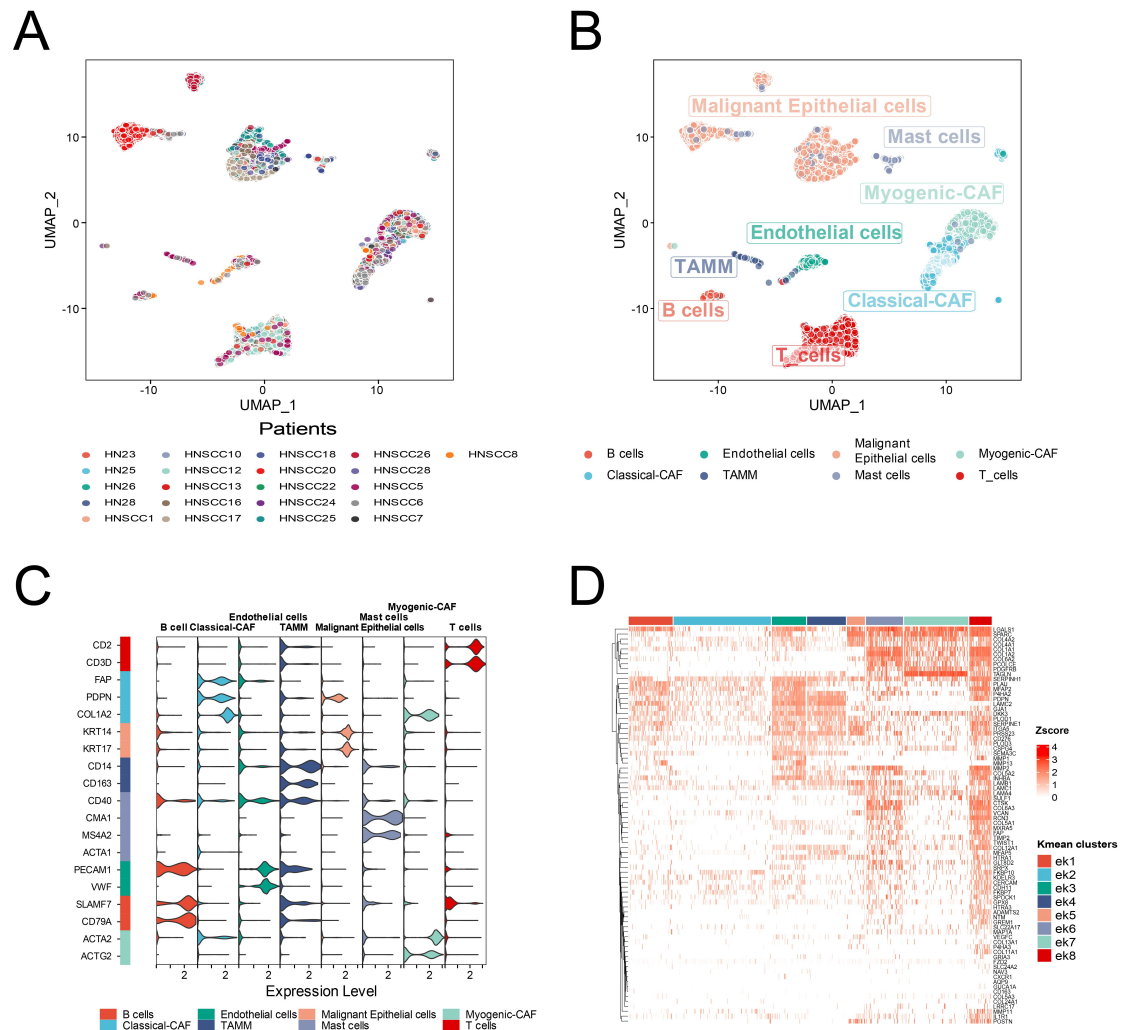


Fig. S6. Single cell annotation of GSE103322. **(A, B)** UMAP plot of GSE103322 single cells, colors represent tissue origin and cell type respectively. **(C)** Expression of marker genes in different cell types. **(D)** Kmean clustering of malignant epithelial, fibroblastic, and endothelial cells in GSE103322 using gene expression in community 1.

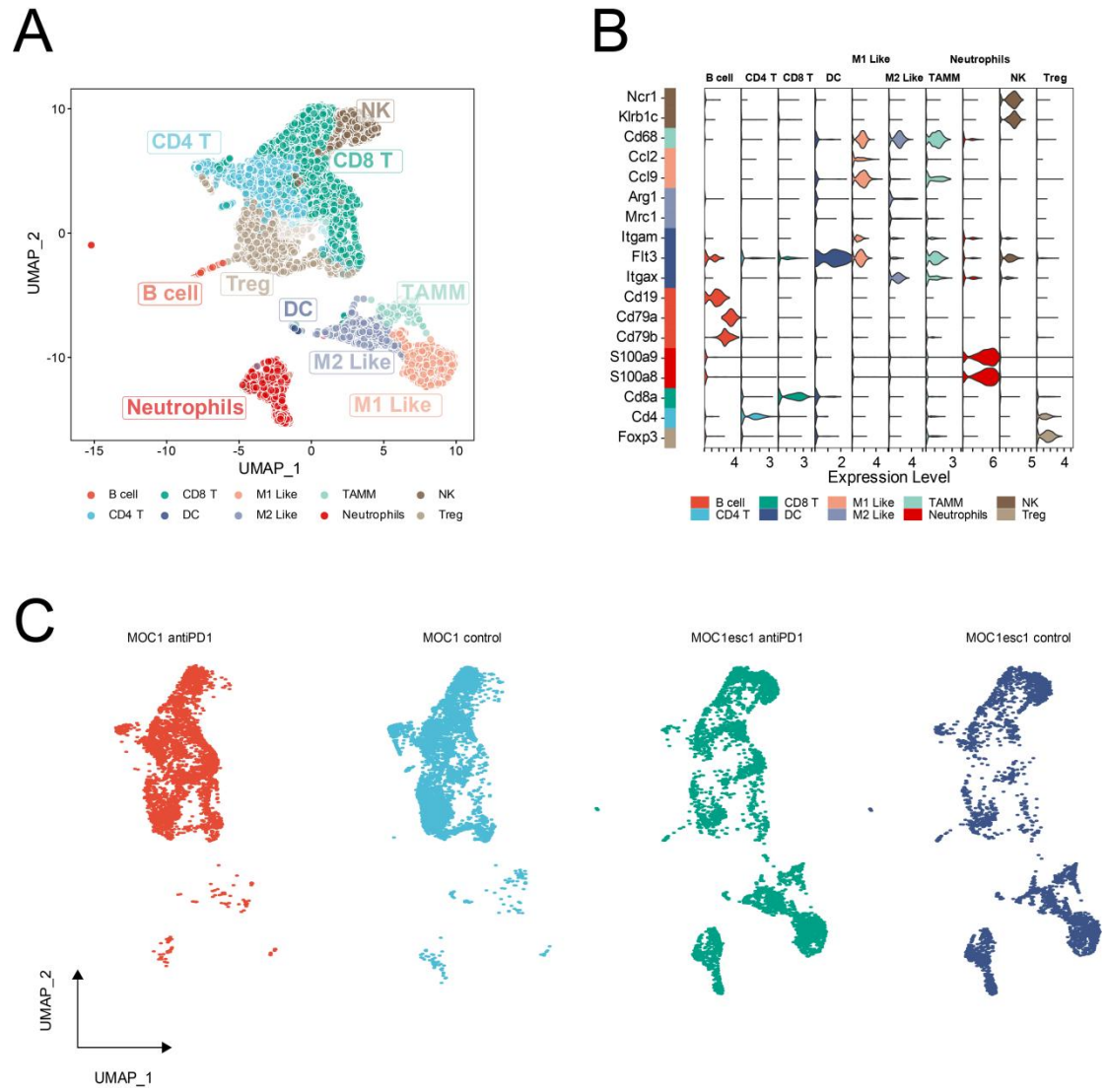


Fig. S7. Single cell annotation of GSE153383. **(A)** UMAP plot of GSE153383 single cells, colors represent cell type. **(B)** Expression of marker genes in different cell types. **(C)** Distribution of GSE153383 cells on UMAP plots under different conditions.

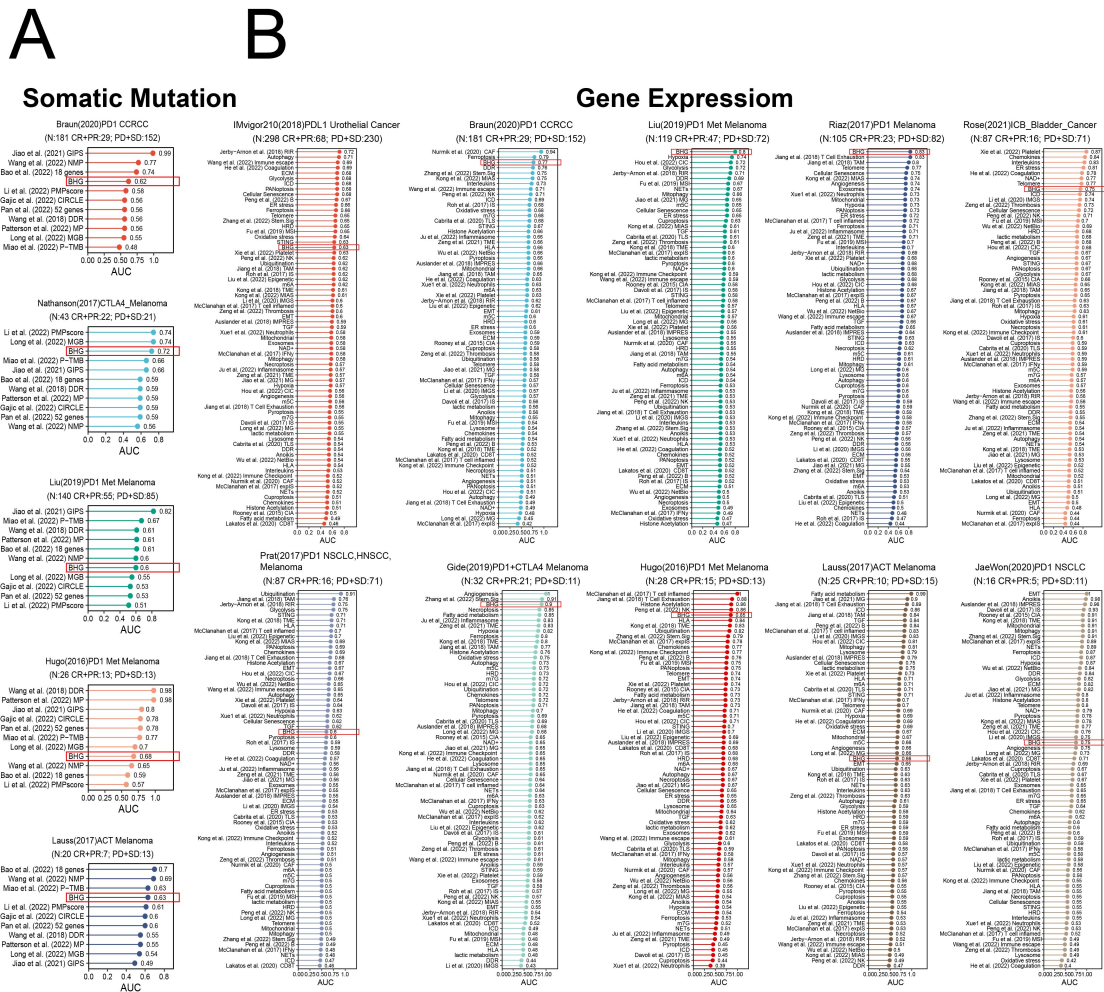


Fig. S8. Comparison of AUC values of BHG with other public gene signatures. **(A)** Comparison of AUC values of BHG with 10 gene signatures at the somatic mutation level for predicting ICI response in 5 ICI cohorts. **(B)** Comparison of AUC values of BHG with 70 gene signatures at the gene expression level for predicting ICI response in 10 ICI cohorts.