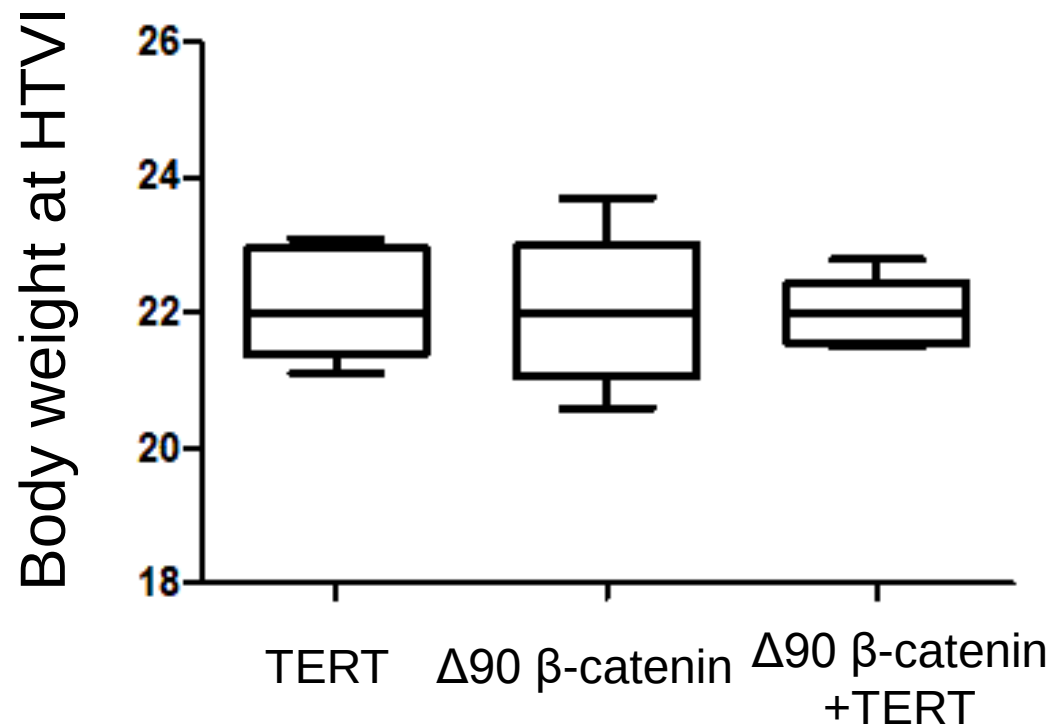
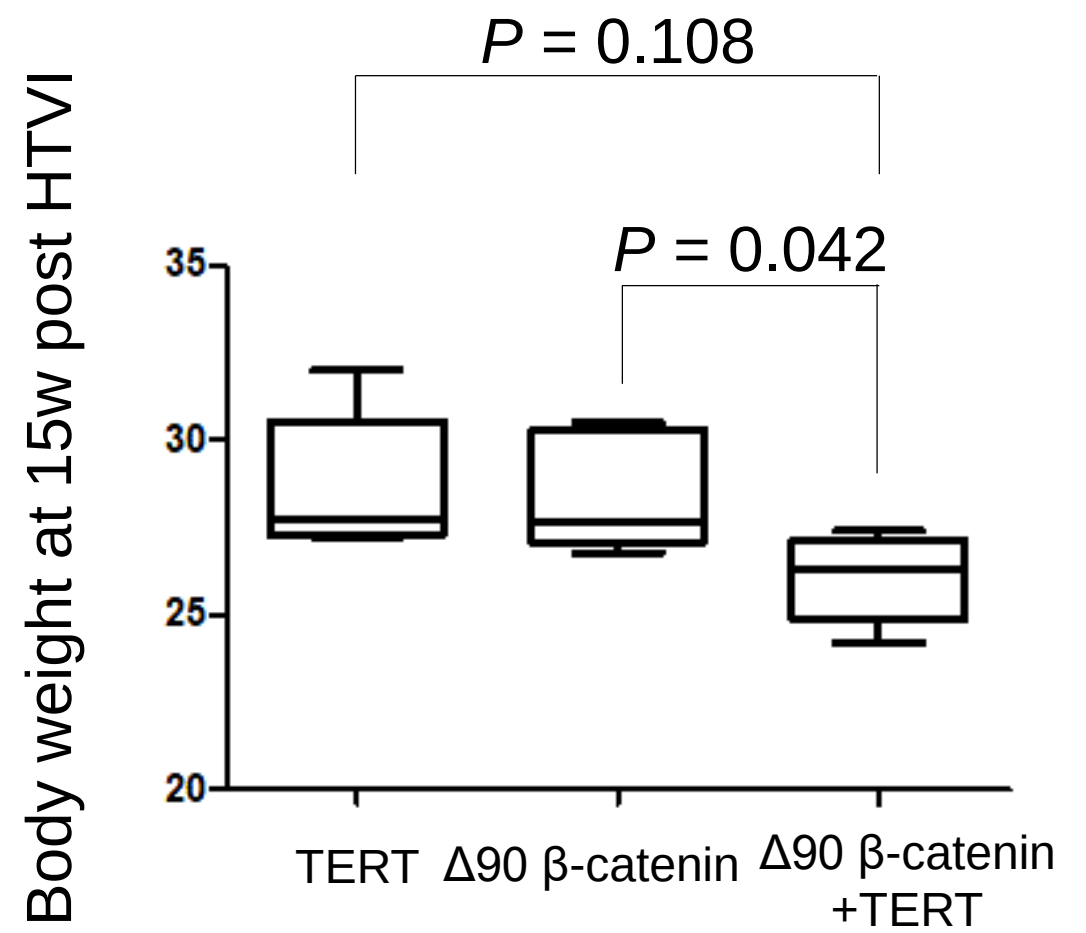


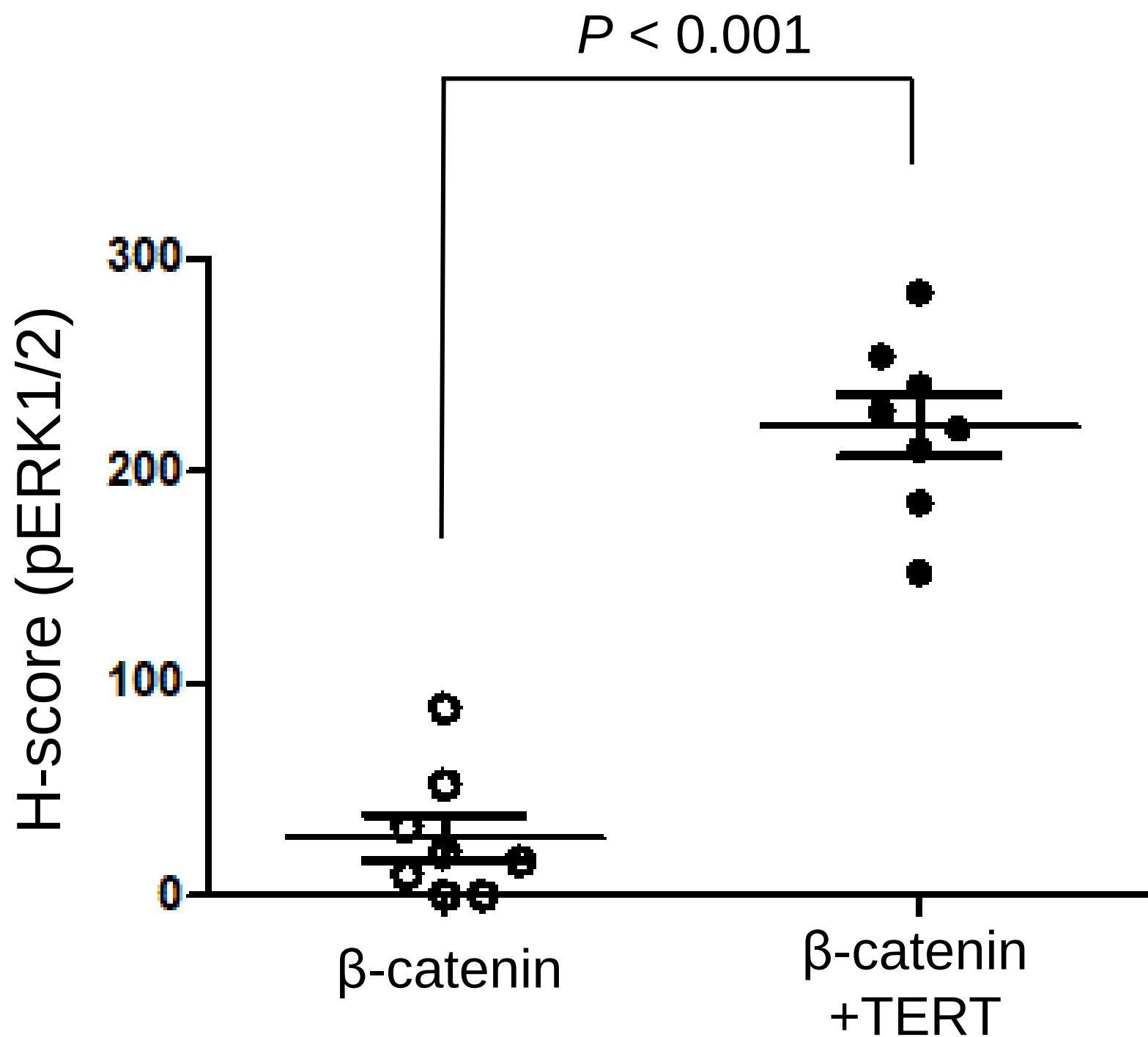
A



B

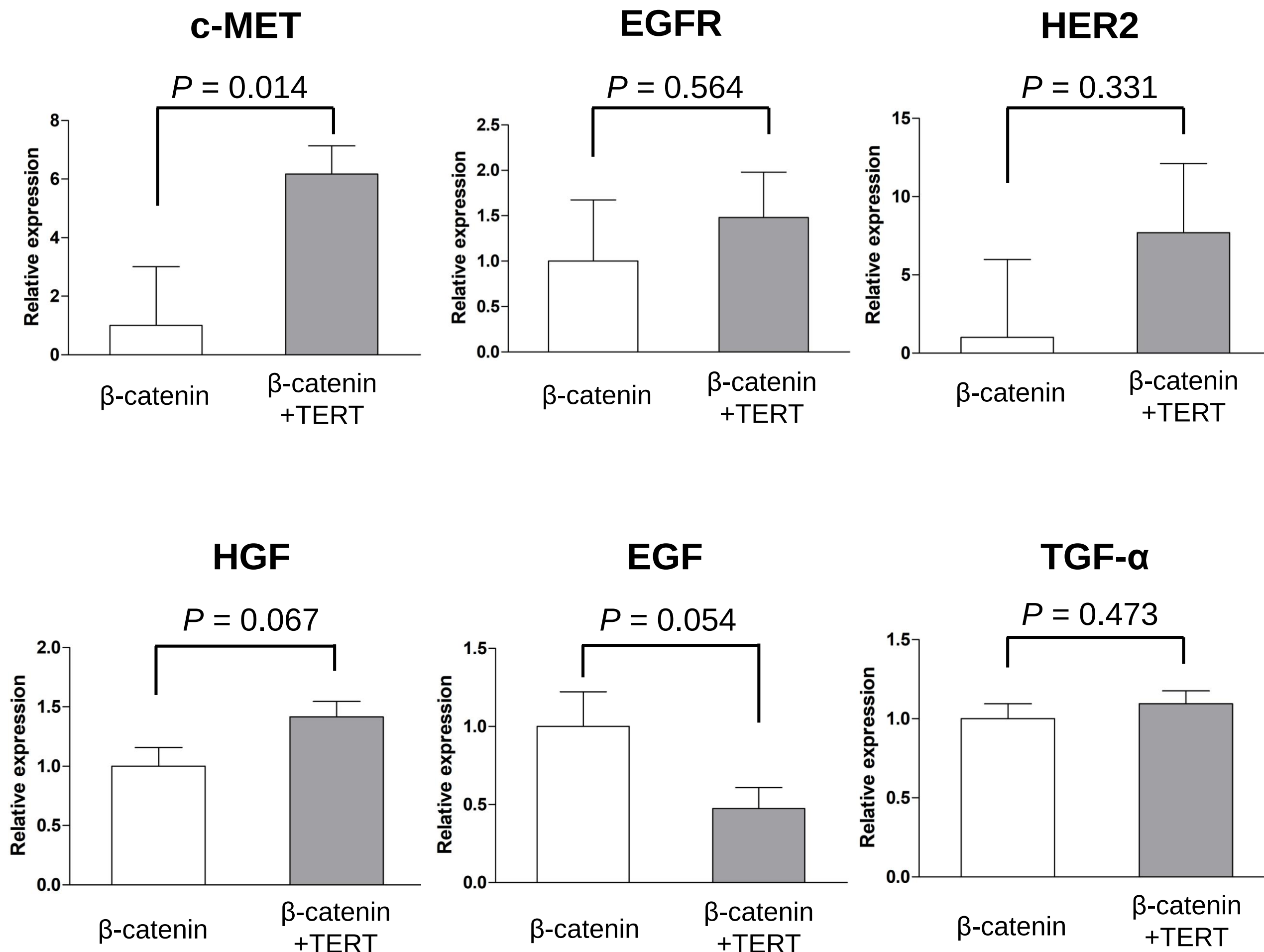


Supplementary Figure S1. Body weights of mice. Body weight was measured at the time of HTVI (A) and at 15 weeks post-HTVI (B). Data are shown as mean $\pm$ SEM. Statistical significance was assessed using Kruskal–Wallis test followed by post hoc pairwise comparisons using Dunn’s test with Bonferroni correction.

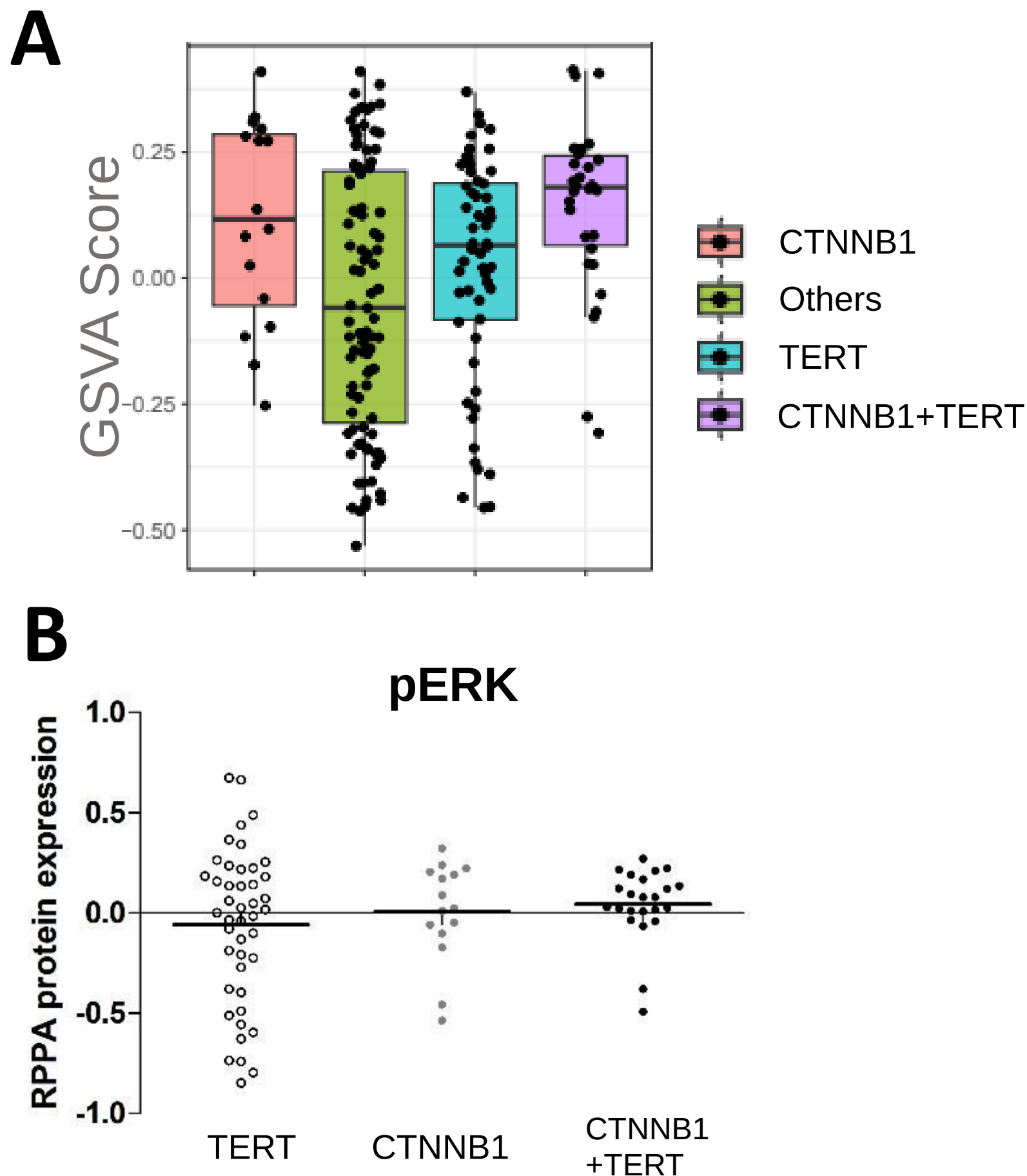


Supplementary Figure S2. Semi-quantitative assessment of pERK1/2 activation by H-score analysis. Quantification of pERK1/2 staining using H-score, incorporating both the percentage of positive tumor cells and staining intensity. Tumors driven by $\Delta 90$ β -catenin and TERT exhibit significantly higher pERK1/2 H-scores compared with $\Delta 90$ β -catenin alone tumors. Data are presented as mean $\pm$ SEM (n = 8 independent tumors per group). Statistical significance was assessed using the Mann–Whitney test.

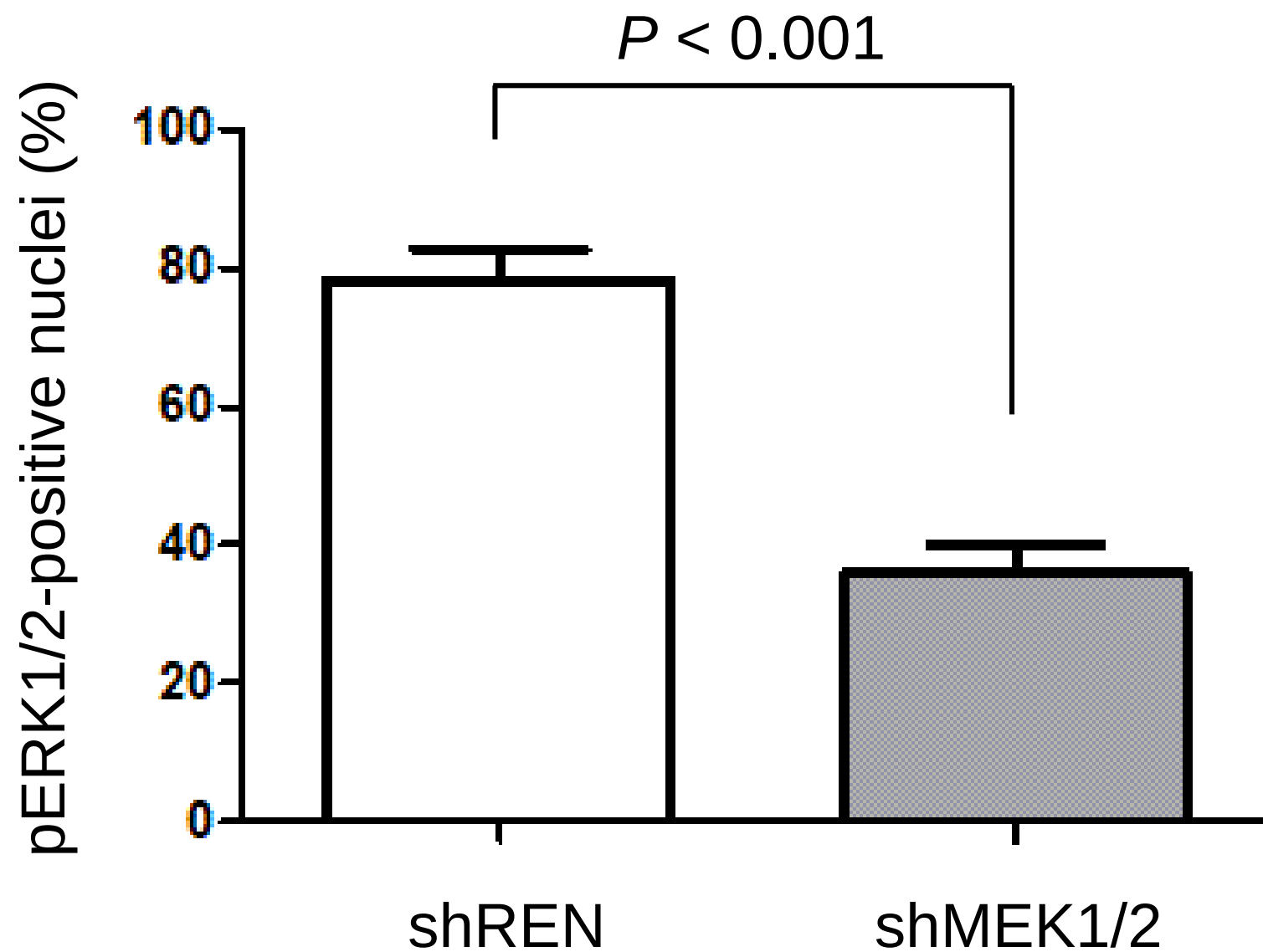
Supplementary Figure S3



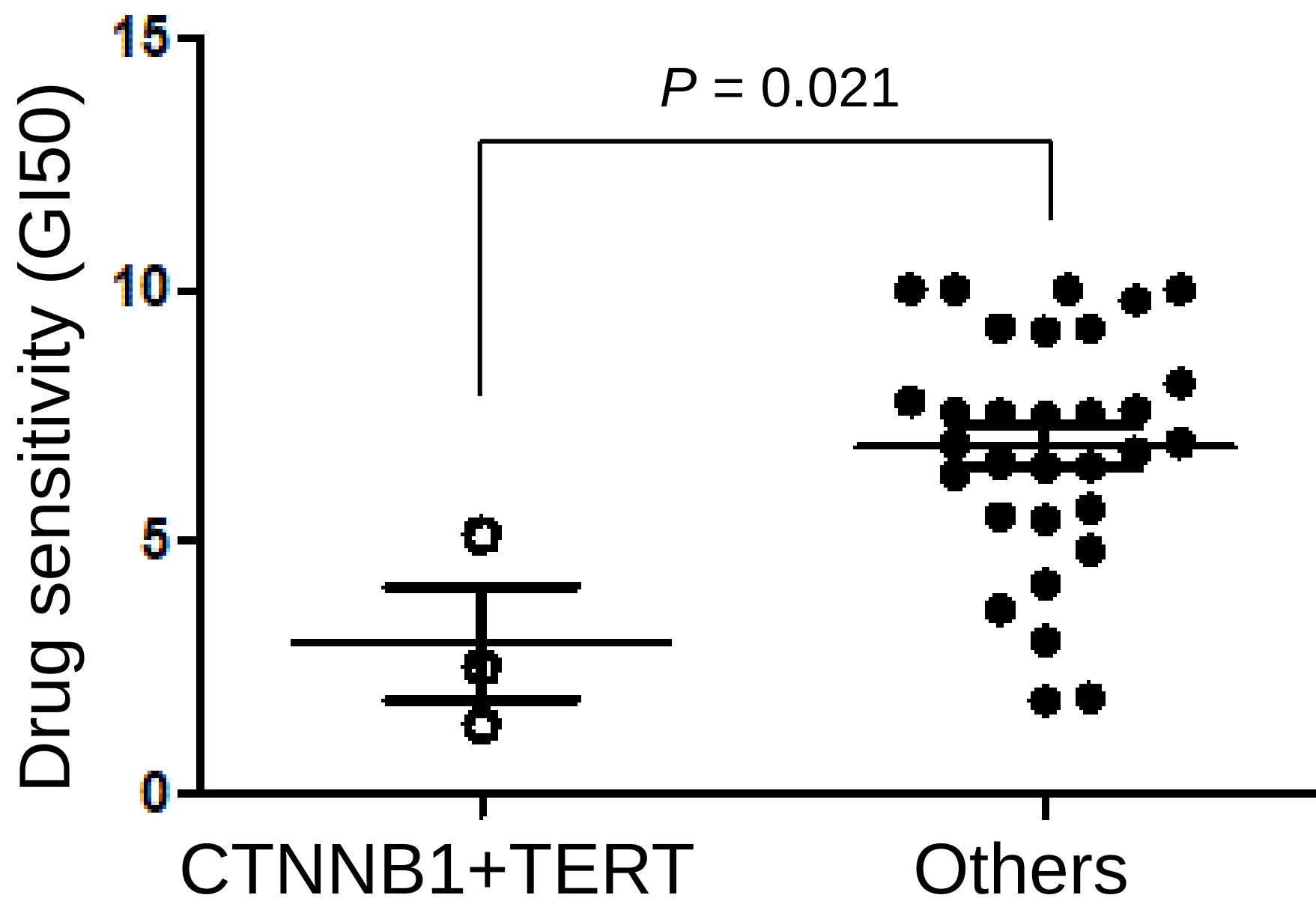
Supplementary Figure S3. Upregulation of c-MET in β -catenin and TERT-driven HCC. mRNA expression levels were assessed via quantitative RT-PCR. Data are presented as mean $\pm$ SEM (n = 5 tumors per group). Statistical significance was assessed using the Mann–Whitney test. HER2, Human epidermal growth factor receptor 2; HGF, Hepatocyte growth factor; EGF, Epidermal growth factor; TGF- α , Transforming growth factor-alpha.



Supplementary Figure S4. MAPK/ERK pathway activity in human HCC stratified by CTNNB1 and TERT mutation status. (A) Transcriptomic analysis of TCGA-LIHC cohort showing MAPK/ERK pathway activity scores (GSVA) in tumors harboring both *CTNNB1* and *TERT* promoter mutations, only *CTNNB1* mutation, only *TERT* promoter mutation, or those with no mutation in *CTNNB1* and *TERT* (labeled as “Others”). No significant differences were observed among groups. (B) Analysis of pERK levels in the HCC subgroups. Tumors with concurrent *CTNNB1* and *TERT* alterations exhibit a trend toward higher pERK levels. The pERK expression data for TCGA-LIHC were obtained from the Clinical Proteomic Tumor Analysis Consortium (CPTAC). Statistical significance was assessed using one-way ANOVA.



Supplementary Figure S5. Quantification of nuclear pERK1/2 staining in shMEK1/2-expressing tumors. Quantification of nuclear pERK1/2 positivity, expressed as the percentage of pERK-positive nuclei across tumor sections. shMEK1/2 tumors show a significant reduction in nuclear pERK staining compared with shREN controls. Data are presented as mean $\pm$ SEM. pERK positivity was determined by counting positive nuclei across 8 independent tumors per group. Statistical significance was assessed using the Mann–Whitney test.



Supplementary Figure S6. Growth inhibition 50% (GI50)-based analysis of sorafenib sensitivity in human liver cancer cell lines. Cell lines harboring concurrent *CTNNB1* and *TERT* mutations (n = 3) showed lower GI50 values compared with the remaining cell lines (n = 31), which include those with either mutation alone or neither mutation. Statistical significance was assessed using the Mann–Whitney test.