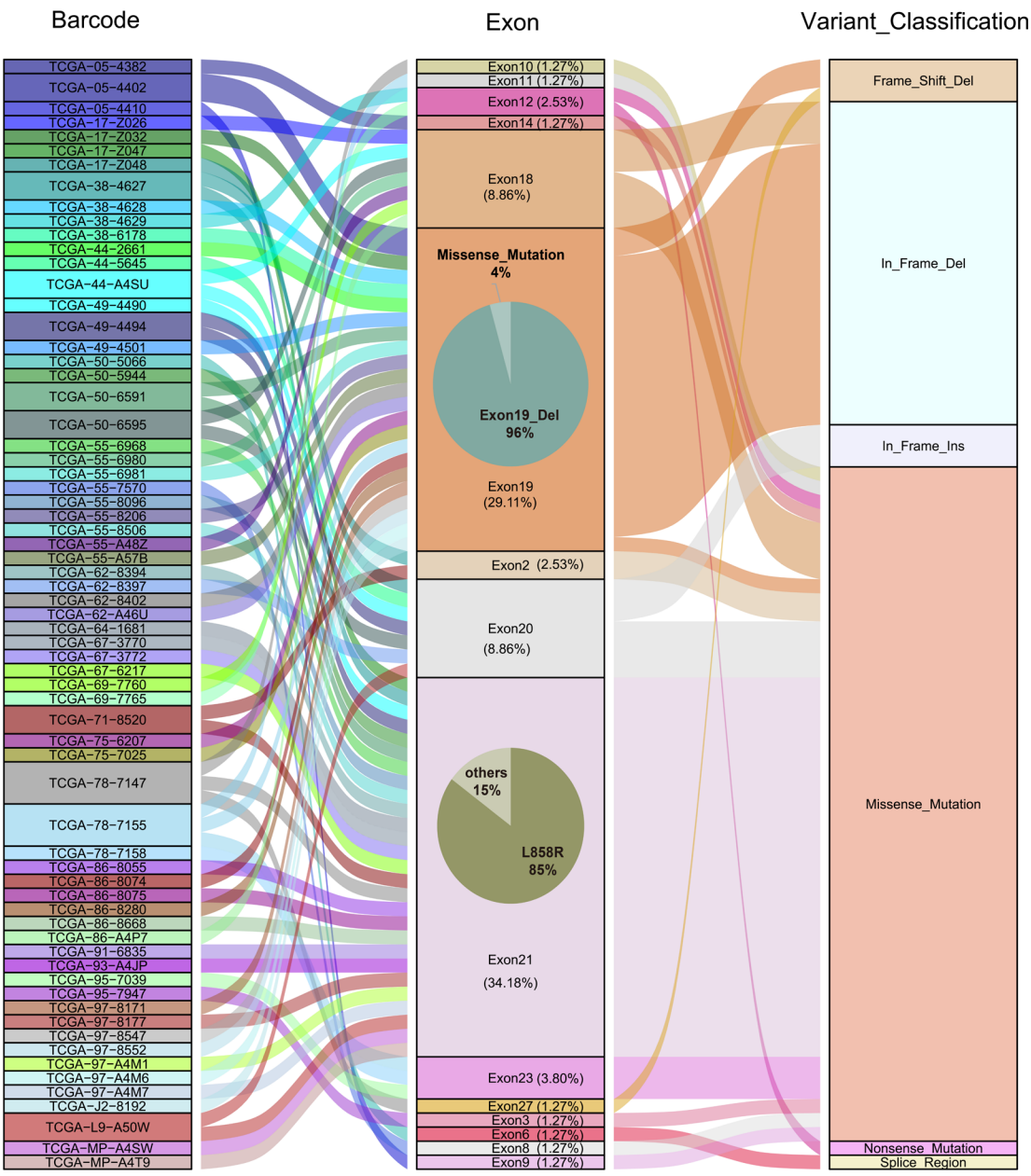

Fig. S1 **Characteristics of Patients with EGFR Mutation.**

The TCGA barcode of patients was shown on the left; the EGFR mutation sites were shown in the middle, and the variant classification was shown on the right. TCGA, The Cancer Genome Atlas Program.

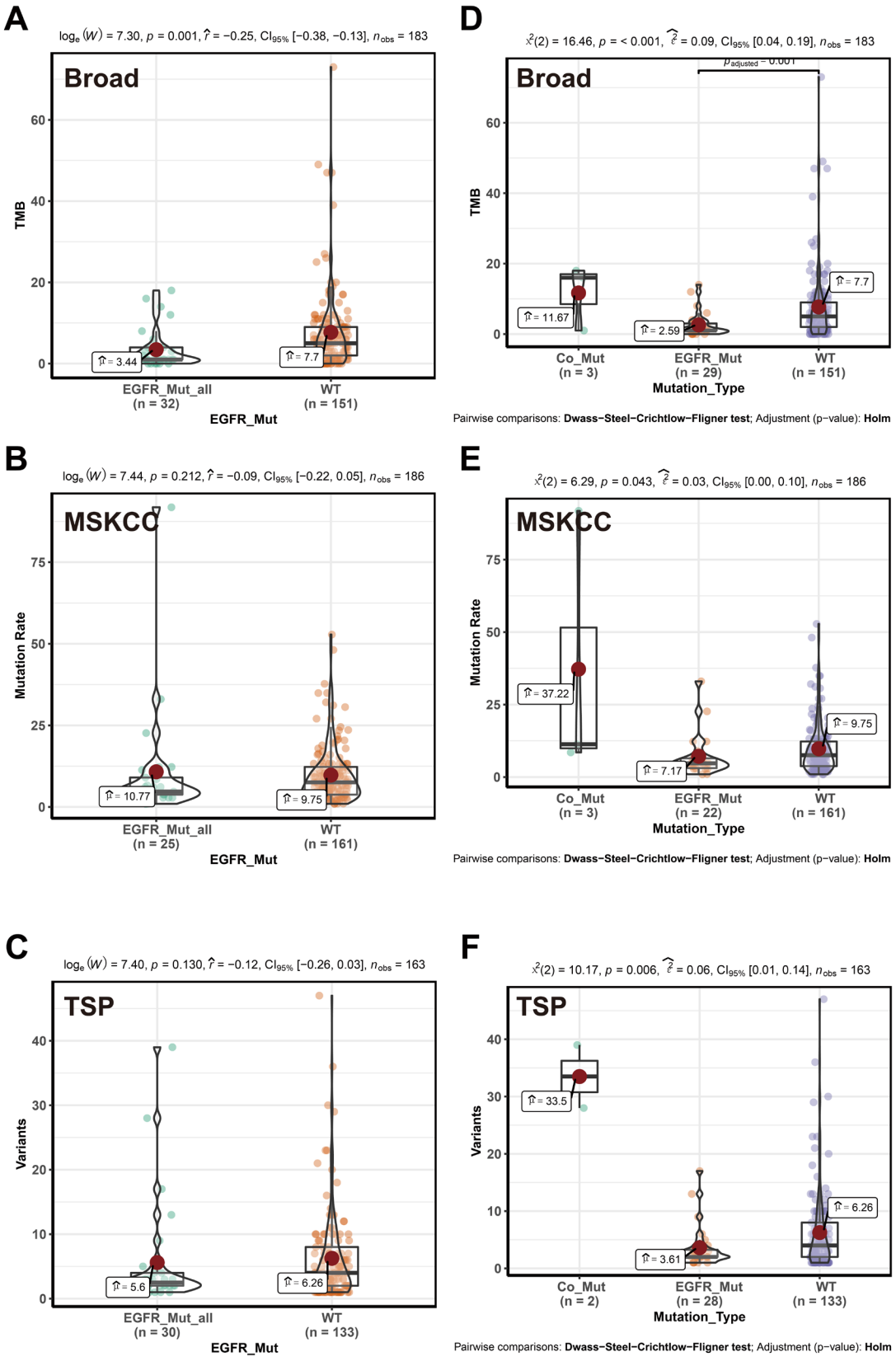

Fig. S2 **TMB Levels in Different Subtypes of Lung Adenocarcinoma.**

The TMB levels between EGFR-mutated and wild type patients in the Broad, MSKCC, and TSP cohort was shown by (A), (B), and (C), respectively. The TMB levels among EGFR-MAPK co-mutated, EGFR mutations, and wild type patients in the Broad, MSKCC, and TSP cohort was shown by (D), (E), and (F), respectively. MSKCC, Memorial Sloan Kettering Cancer Center; TSP, The Tumour Sequencing Project.

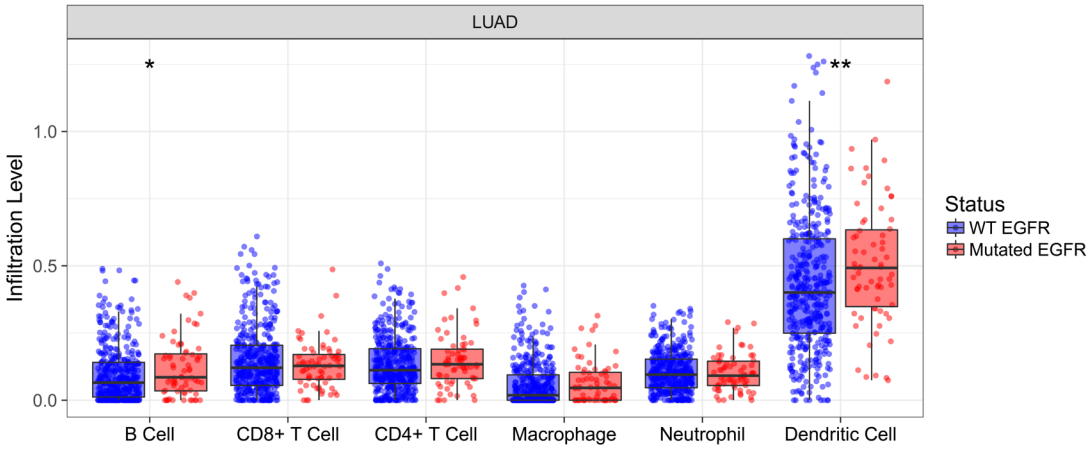

Fig. S3 **The levels of Immune Infiltrates of EGFR-Mutated patients in TIMER.** Blue represented wild-type LUAD patients, and red represented EGFR mutation patients. P-value Significant Codes: 0 ≤ *** < 0.001 ≤ ** < 0.01 ≤ * < 0.05. LUAD, lung adenocarcinoma.

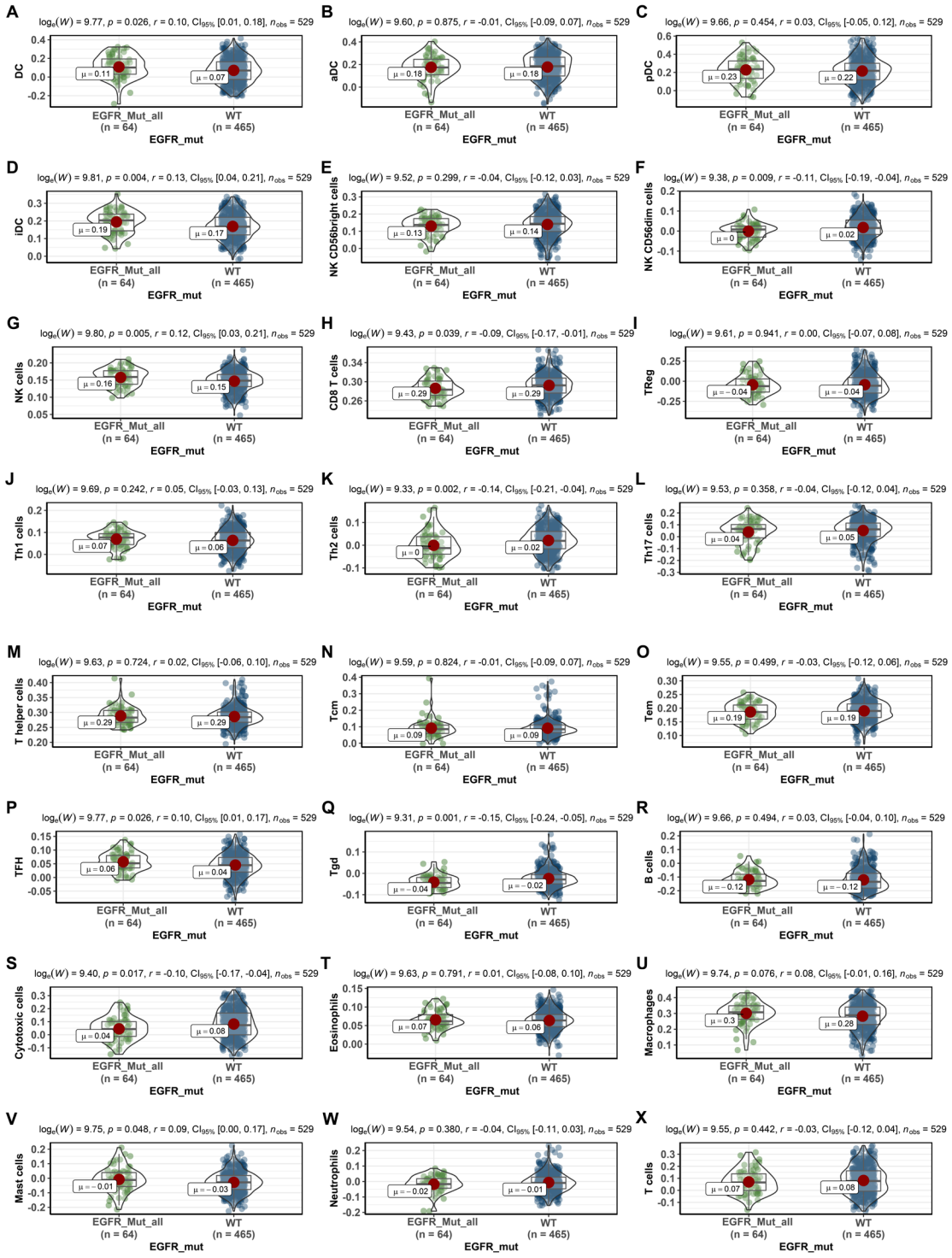

Fig. S4 **The Level of Immune Infiltration between EGFR-mutated and Wild-type Patients.**

The violin diagram showed the level of immune infiltration between EGFR-mutated and wild-type patients. (A) DC; (B) aDC; (C) pDC; (D) iDC; (E) NK CD56bright cells; (F) NK CD56dim cells; (G) NK cells; (H) CD8 T cells; (I) TReg; (J) Th1 cells; (K) Th2 cells; (L) Th17 cells; (M) T helper cells; (N) Tcm; (O) Tem; (P) TFH; (Q) Tgd; (R) B cells; (S)

Cytotoxic cells; (T) Eosinophils; (U) Macrophages; (V) Mast cells; (W) Neutrophils; (X) T cells. DC, dendritic cell; aDC, activated DCs; pDC, plasmacytoid DCs; iDC, immature DCs; Th cells, T helper cells; Tcm, T central memory cell; Tem, T effector memory cell; TFH, T follicular helper cell; Tgd, T gamma delta; TReg, regulatory T cell.

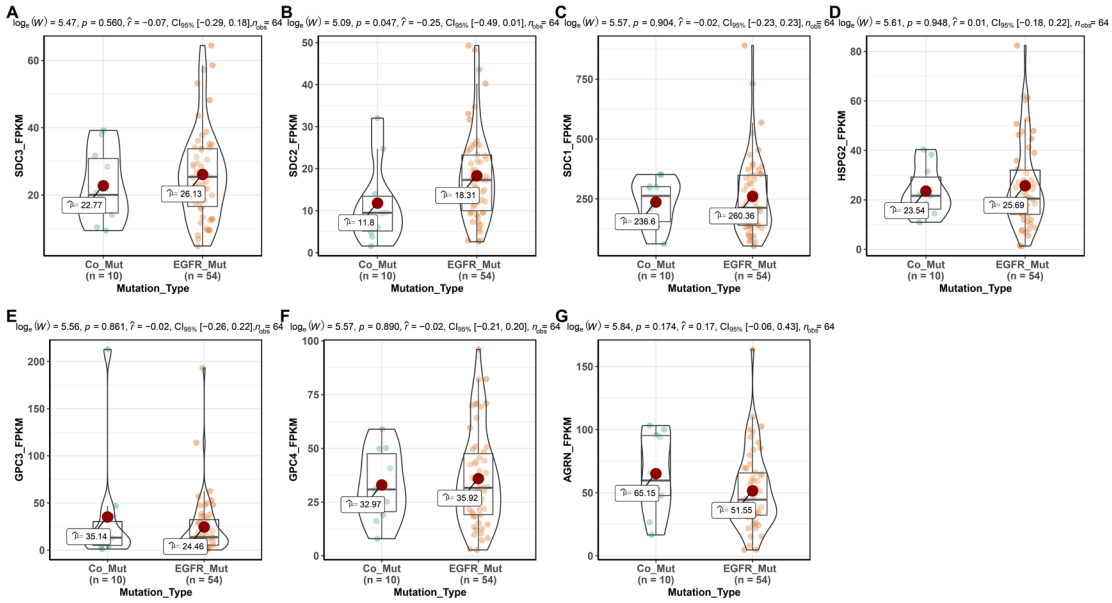

Fig. S5 **Expression Levels of Seven Key Genes in GAG-related Pathways.**

The violin diagram showed the expression levels of seven key genes of the GAG-related pathways in patients with co-mutation and EGFR mutations. (A) SDC3; (B) SDC2; (C) SDC1; (D) HSPG2; (E) GPC3; (F) GPC4; (G) AGRN. SDC3, Syndecan-3; SDC2, Syndecan-2; SDC1, Syndecan-1; HSPG2, Heparan Sulfate Proteoglycan 2; GPC3, Glypican-3; GPC4, Glypican-4; AGRN, Agrin.

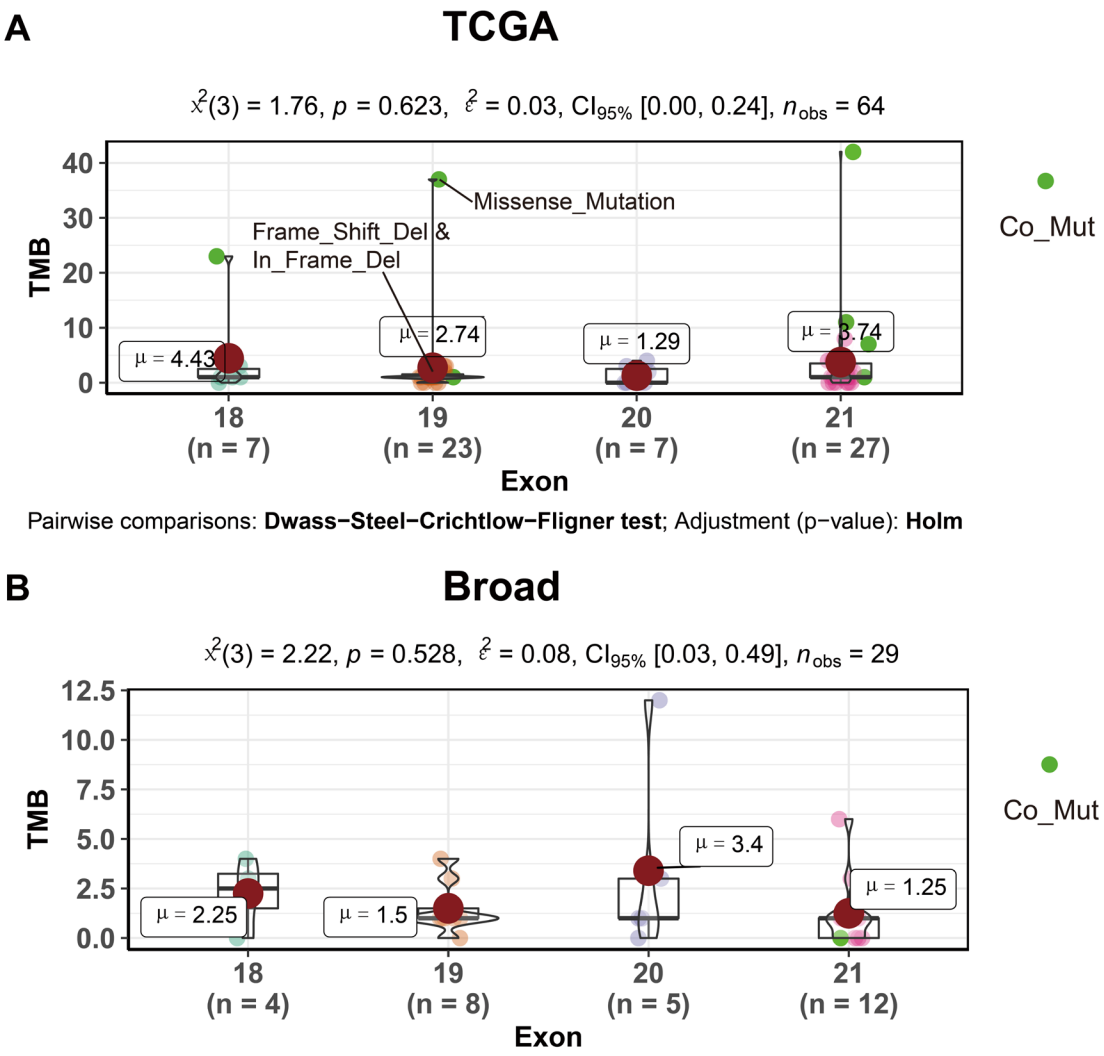

Fig. S6 **The Tumor Mutation Burden Levels of Patients with EGFR Exon 18-21 Mutation.**

The violin diagram showed the level of TMB among patients with EGFR exon 18-21 mutations. (A) Data from TCGA; (B) Data from Broad. TCGA, The Cancer Genome Atlas Program. Co_Mut, EGFR-MAPK co-mutated patients.

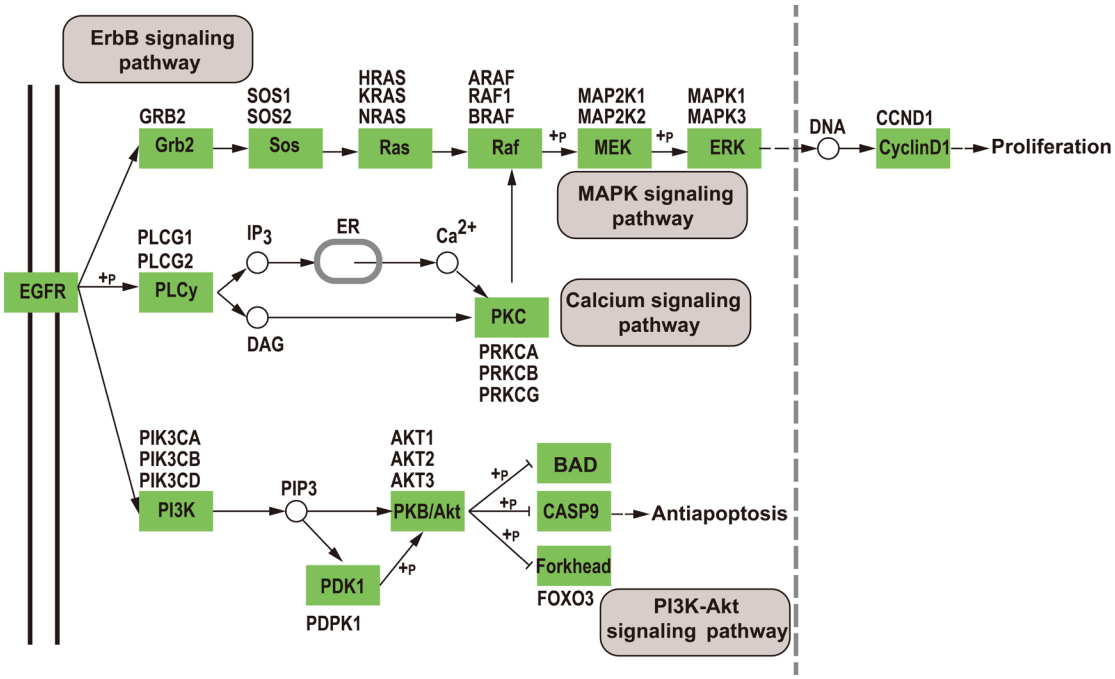

Fig. S7 **EGFR Downstream Pathways in Non-small Cell Lung Cancer.**

EGFR downstream signal transduction pathway mainly included the MAPK signaling pathway, calcium signaling pathway, and PI3K-Akt signaling pathway.

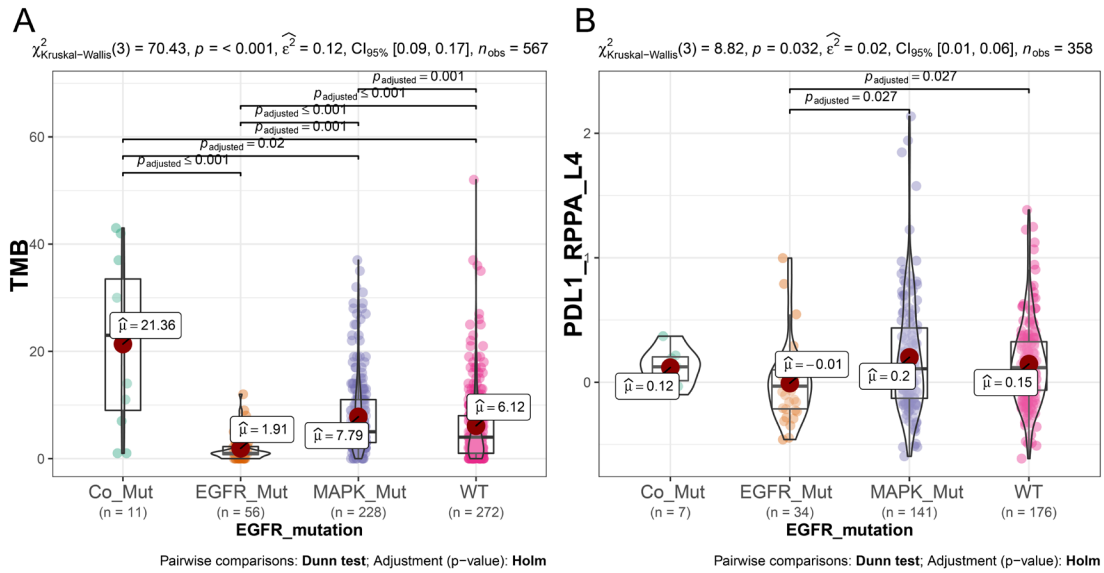

Fig. S8 **TMB and PD-L1 Protein Levels in Different EGFR-MAPK Mutation Subtypes of Lung Adenocarcinoma.**

(A - B) showed TMB and PD-L1 protein levels among Co_Mut, EGFR-mutated, MAPK_Mut, and wild-type patients, respectively. Co_Mut, EGFR-MAPK co-mutated

patients; EGFR_Mut, EGFR-mutated patients; MAPK_Mut, patients with MAPK signaling geneset mutations; WT, wild-type patients.

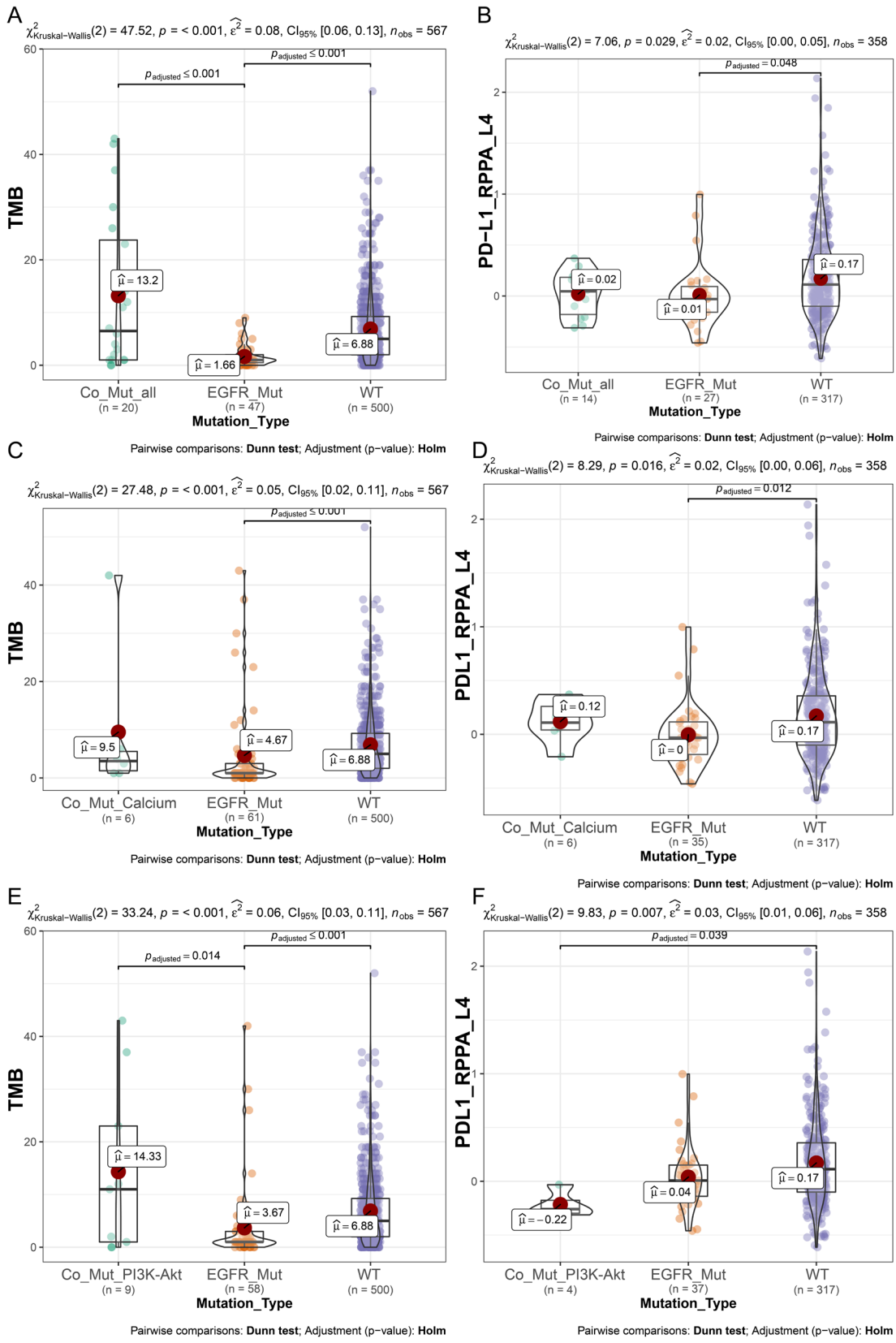

Fig. S9 **TMB and PD-L1 Protein Levels of Different Co-mutation Criteria.**

(A - B) showed TMB and PD-L1 protein levels among Co_Mut_all, EGFR-mutated, and wild-type patients, respectively; (C-D) showed TMB and PD-L1 protein levels among Co_Mut_Calcium, EGFR-mutated, and wild-type patients, respectively; (E-F) showed TMB and PD-L1 protein levels among EGFR-PI3K-Akt, EGFR-mutated, and wild-type patients, respectively. Co_Mut_all, EGFR, and its downstream genes co-mutated patients; Co_Mut_Calcium, EGFR, and Calcium-signaling genes co-mutated patients; Co_Mut_PI3K-Akt, EGFR, and PI3K-Akt-signaling genes co-mutated patients; EGFR_Mut, EGFR-mutated patients; WT, wild-type patients.

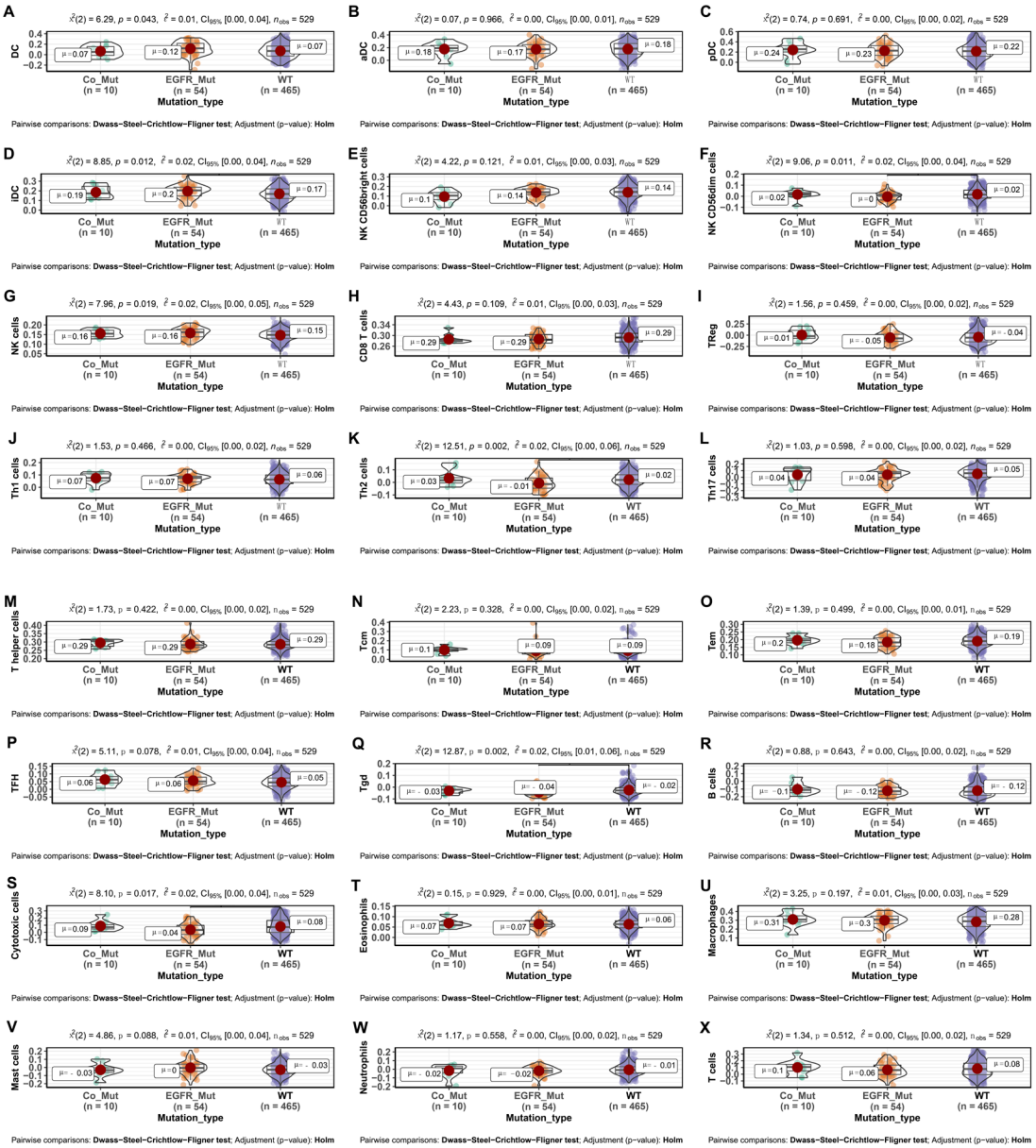

Fig. S10 **Single Sample Gene Set Enrichment Analysis of Different EGFR Mutation Types.**

The violin diagram showed the level of immune infiltration among EGFR-MAPK co-mutated, EGFR-mutated and wild-type patients. (A) DC; (B) aDC; (C) pDC; (D) iDC; (E) NK CD56bright cells; (F) NK CD56dim cells; (G) NK cells; (H) CD8 T cells; (I) TReg; (J) Th1 cells; (K) Th2 cells; (L) Th17 cells; (M) T helper cells; (N) Tcm; (O) Tem; (P) TFH; (Q) Tgd; (R) B cells; (S) Cytotoxic cells; (T) Eosinophils; (U) Macrophages; (V) Mast cells; (W) Neutrophils; (X) T cells. DC, dendritic cell; aDC, activated DCs; pDC, plasmacytoid DCs; iDC, immature DCs; Th cells, T helper cells; Tcm, T central memory cell; Tem, T effector memory cell; TFH, T follicular helper cell; Tgd, T gamma delta; TReg, regulatory T cell.

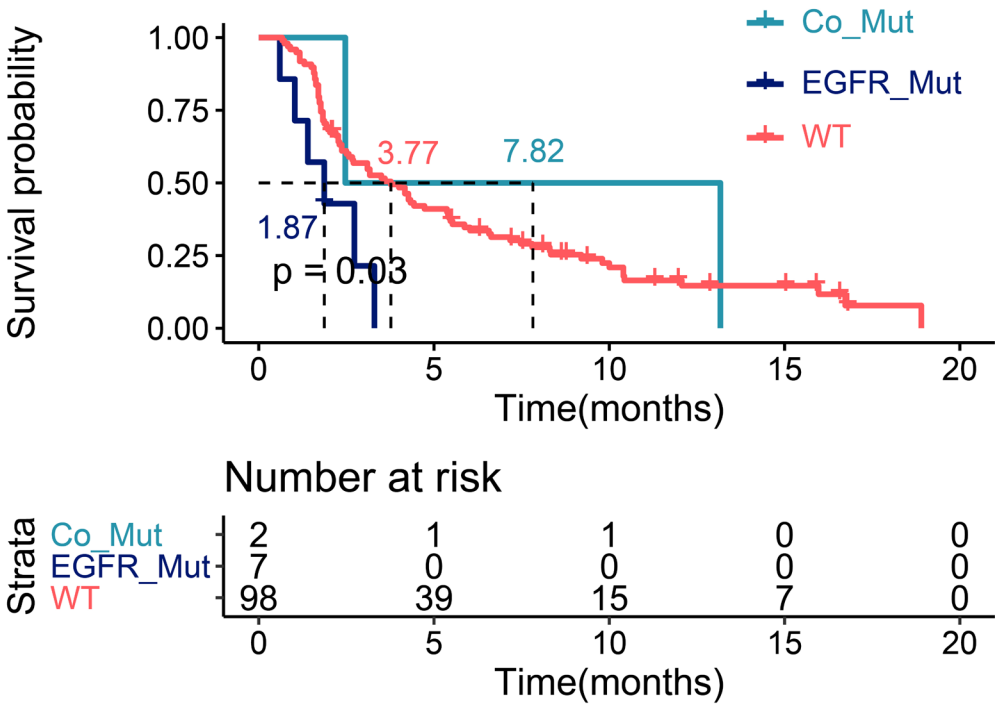

Fig. S11 **The Kaplan-Meier Plot of Progression-free Survival.**

Patients with EGFR-MAPK co-mutations and wild-type patients had better outcomes than patients with EGFR mutations. Green represented the EGFR-MAPK co-mutated patients; dark blue represented EGFR-mutated patients, and red represented wild-type patients (p-value = 0.03). Co_Mut, EGFR-MAPK co-mutated patients; EGFR_Mut, EGFR-mutated patients; WT, wild-type patients.