

Supplementary figures:

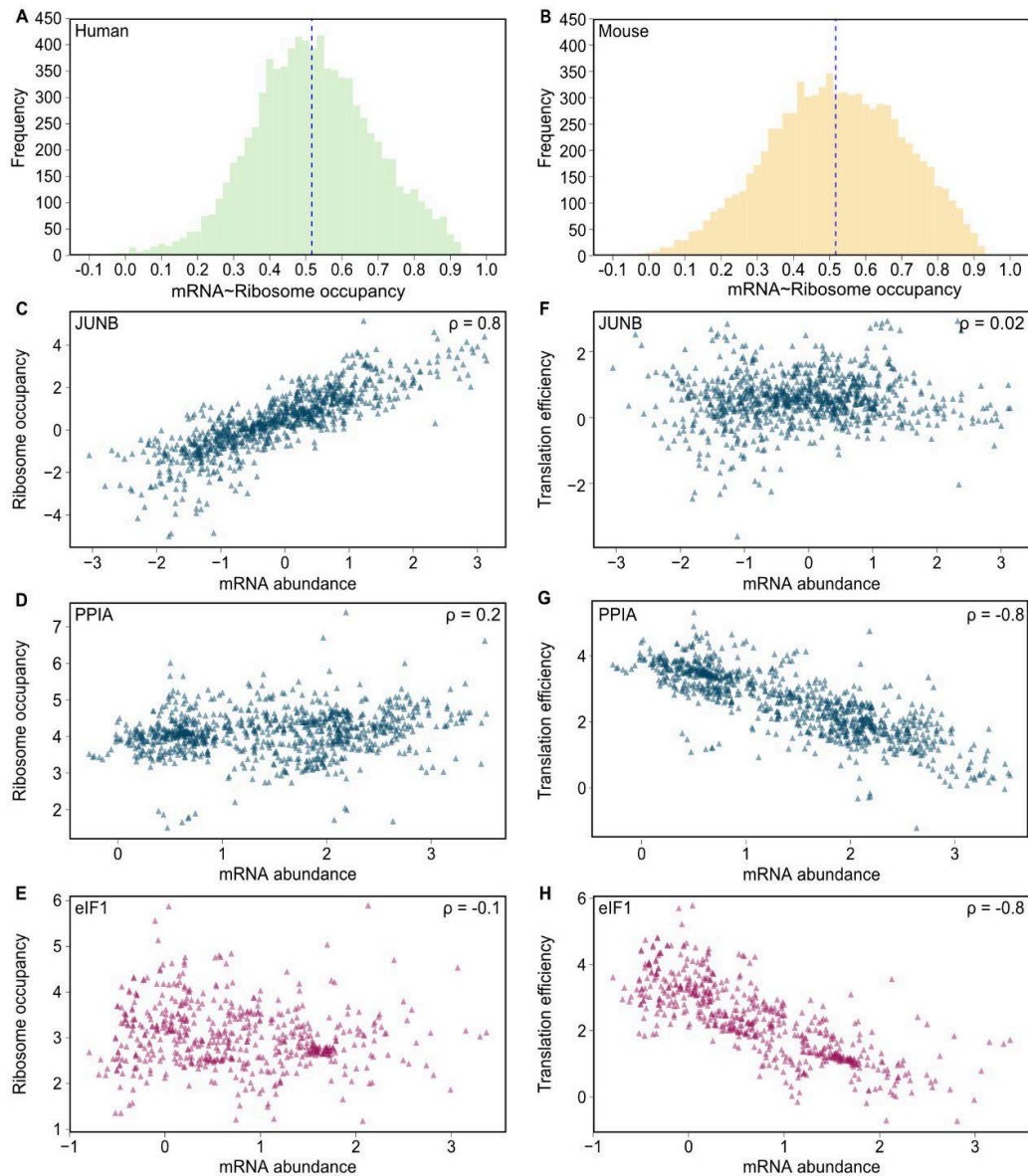


Fig. S1: **A.** Spearman correlation between mRNA abundance and ribosome occupancy calculated from ribosome profiling and matched RNA-seq of 965 human samples for 8433 human genes **B.** Spearman correlation between mRNA abundance and ribosome occupancy calculated from ribosome profiling and matched RNA-seq of 550 mouse samples for 8135 mouse genes. Relationship between mRNA abundance and ribosome occupancy of a **C.** human non-buffered gene; JUNB **D.** human buffered gene; PPIA, **E.** mouse buffered gene; eIF1. Relationship between mRNA abundance and translation efficiency of a **F.** human non-buffered

gene; JUNB, **G.** human buffered gene; PPIA, **H.** mouse buffered gene; eIF1. Each point is the information from a ribosome profiling and matched RNA-seq experiment for the given gene.

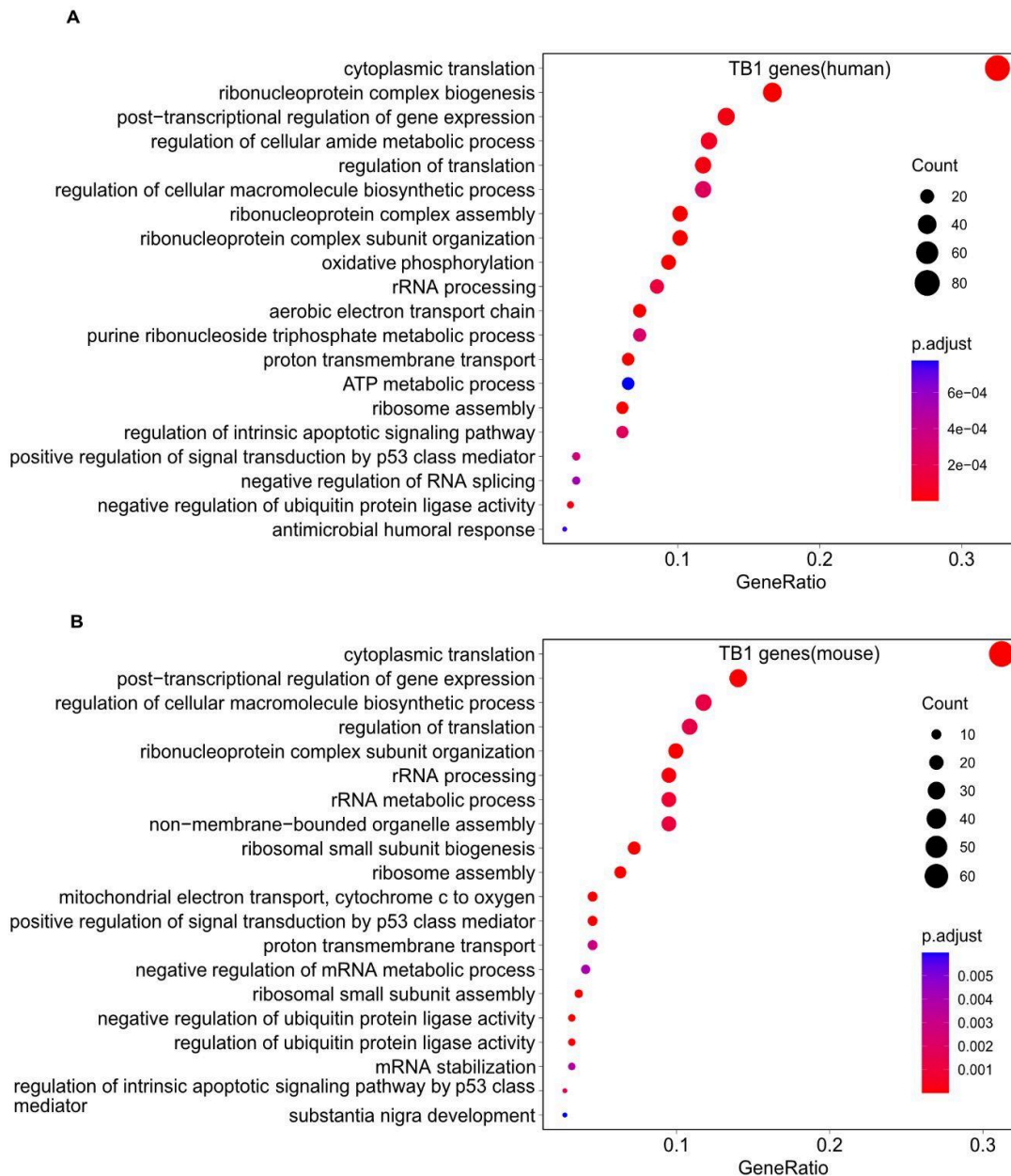


Fig. S2 Gene Ontology (GO) enrichment analysis of the TB high gene set, performed with the clusterProfiler R package. Enriched GO Biological Process terms are shown after redundancy reduction for **A.** Human , **B.** Mouse. Each dot represents a GO term, with dot size indicating the

number of genes associated with the term and color reflecting the adjusted p-value (Benjamini–Hochberg correction). Only the top non-redundant terms are displayed.

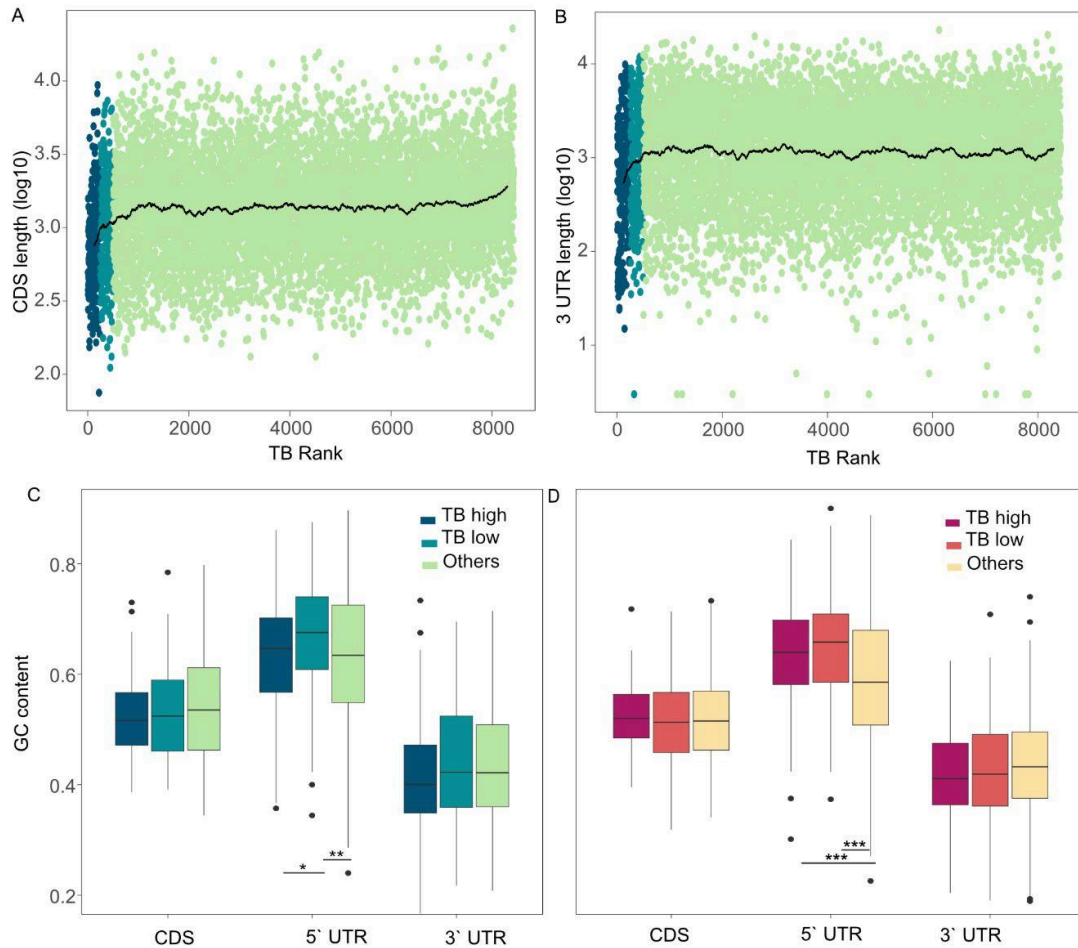


Fig. S3. Scatter plot showing the relation between rank and **A.** CDS length and **B.** 3' UTR length. A moving average of CDS or 3' length was calculated using a centered 250-gene sliding window and is shown as the black line. Box plot showing the GC content of CDS, 5'-UTR and 3'-UTR of the three categories (TB high, low and others) of **C.** human genes (TB high; n=250, TB low; n= 245; others; n=495) **D.** mouse genes (TB high; n=250, TB low; n= 250; others; n=500) The y axis indicates GC content. Gene in the "other" category were selected after a matching approach (See Methods). The * indicate p values. * < 1×10^{-3} , ** < 1×10^{-4} , *** < 1×10^{-5} .

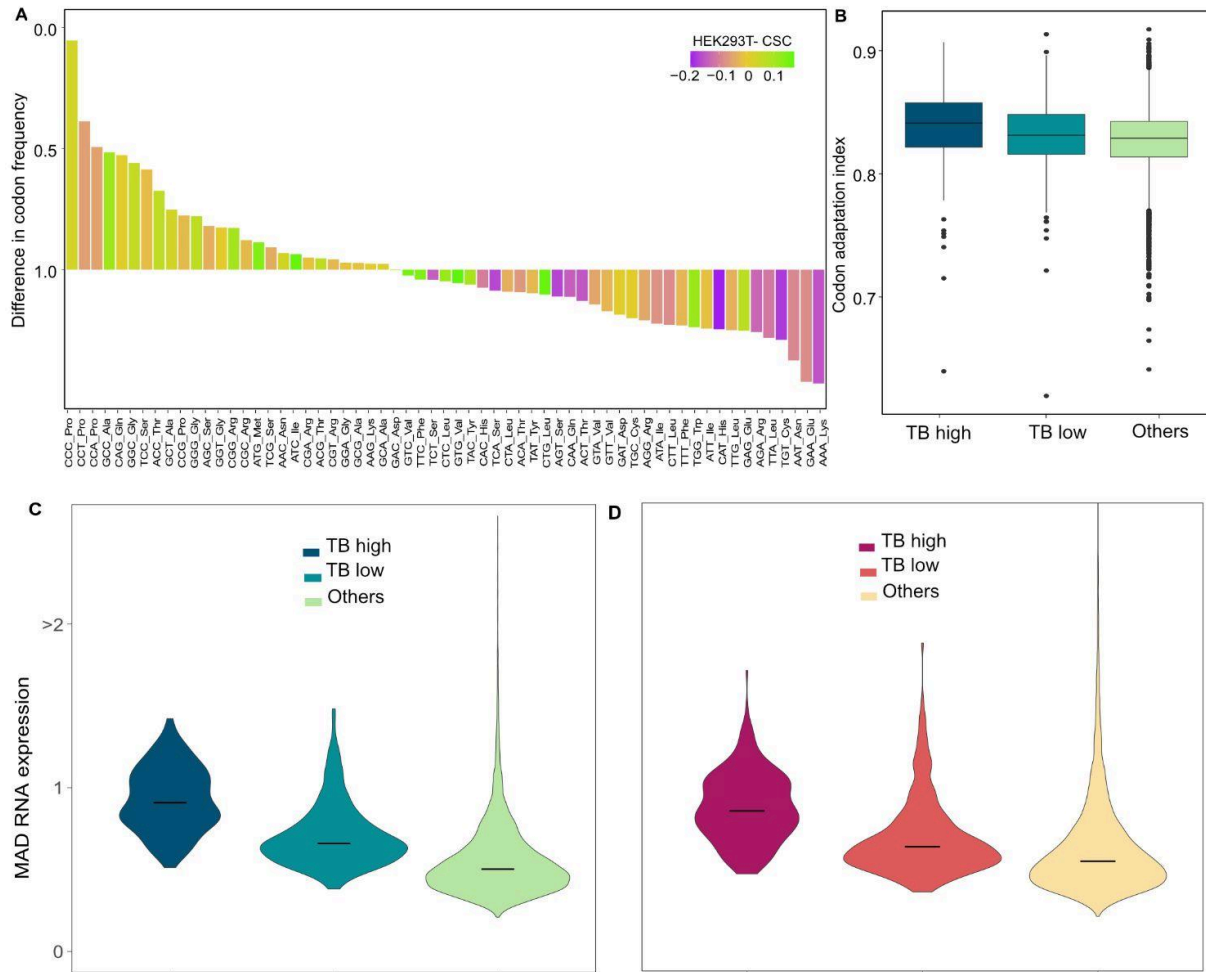


Fig. S4: **A.** Bar plot showing the difference in codon frequency between “low” and non-buffered genes. The bars are colored according to the codon stabilization coefficient obtained from [29]. *n* refers to the number of genes. **B.** Box plot showing the codon adaptation index of human genes belonging to three categories. (TB high; *n*=250, TB mid; *n*= 250; Others; *n*= 7934). **C.** Violin plot showing the median absolute deviation of mRNA abundance of genes in all three categories in human (TB high; *n*=250, TB low; *n*= 250; others; *n*=7933). **D.** Violin plot showing the median absolute deviation of mRNA abundance of genes in all three categories in mouse (TB high; *n*=250, TB low; *n*= 250; others; *n*=7635). *n* refers to the number of genes.

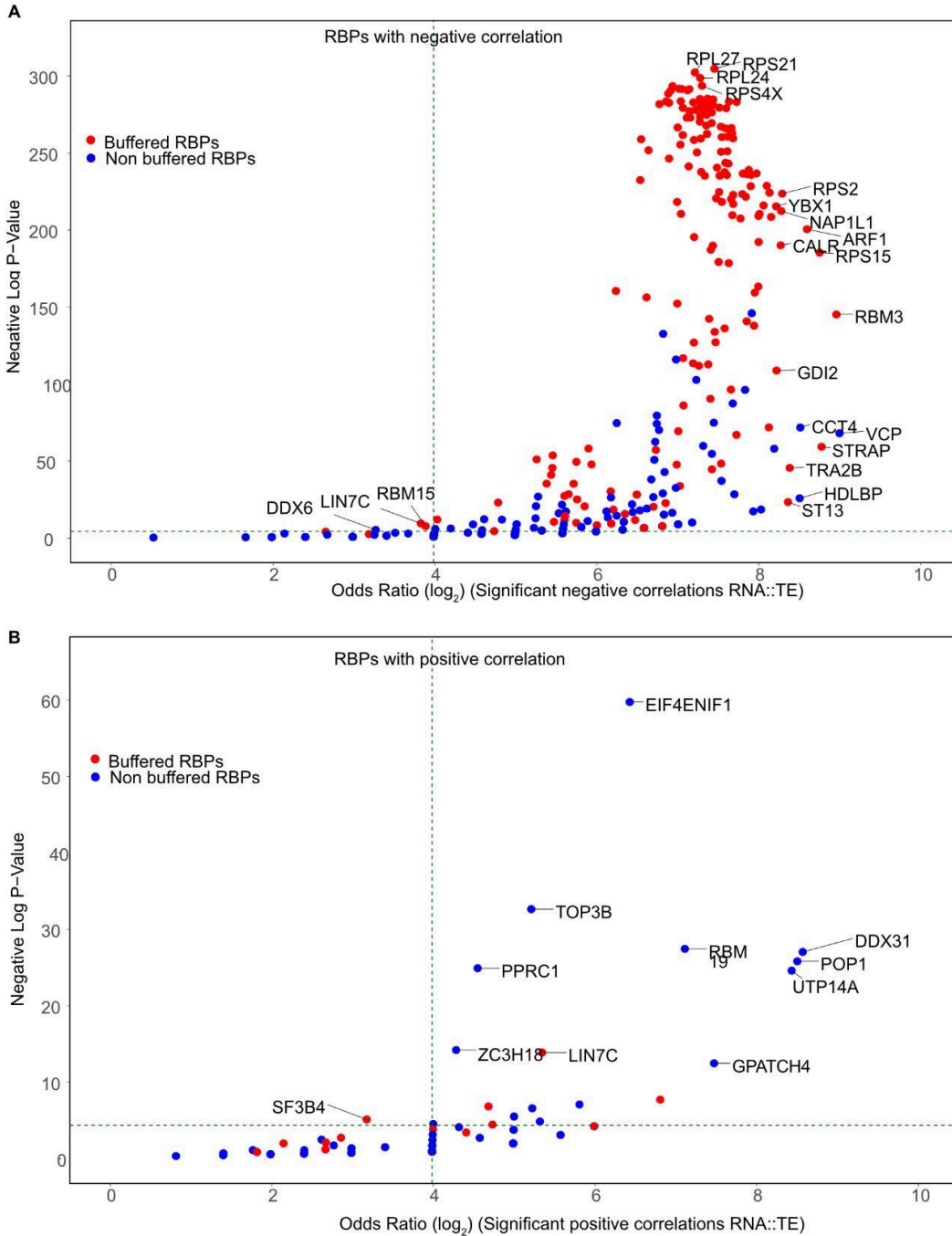


Fig. S5: A scatter plot of odds ratio $\log_2$ of number of significant correlations (RNA abundance of RBPs ::TE of genes) and the p value from fisher test **A.** RBP with negative correlations **B.** RBP with positive correlations. The vertical dashed line represents the threshold odds ratio, above which RBPs exhibit a higher number of significant correlations with buffered genes. P values were corrected using Bonferroni procedure and the horizontal dashed line represents the adjusted p value cutoff.

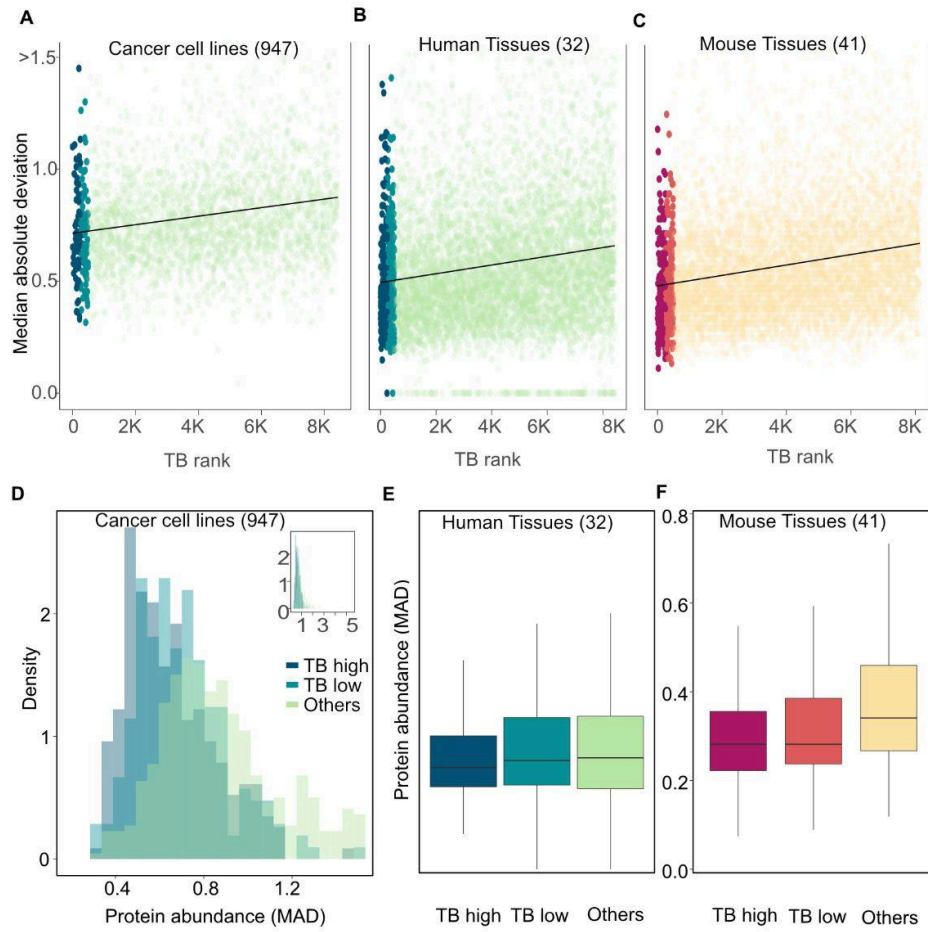


Fig. S6: Scatter plot showing the relation between rank and median absolute deviation of proteins in **A.** Cancer cell line **B.** Human tissues **C.** Mouse tissue. Linear regression trend line is shown in black. Boxplot showing the MAD of protein abundance of genes with non-buffered genes selected with similar mRNA MAD as the buffered genes from **D.** human cancer cell lines from [34] (TB high; n=221, TB mid; n= 202; Others; n= 423) **E.** human primary tissue from [35] (TB high; n=233, TB mid; n= 227; Others; n= 460) and **F.** mouse tissues from [36] (TB high; n=189 TB mid; n= 199; Others; n=388). Genes selected in the “Others” category were derived by a matching procedure (Methods). n refers to the number of genes

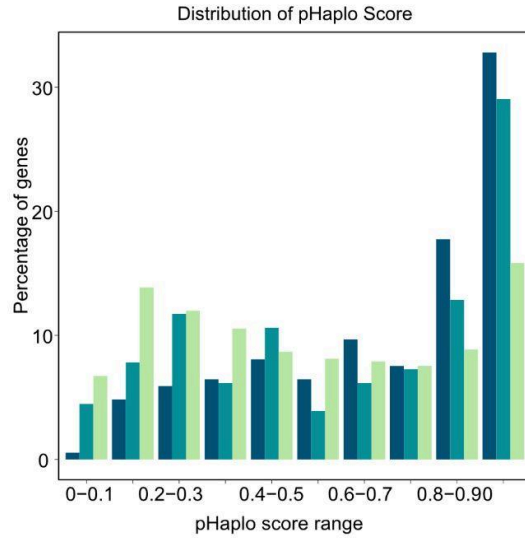


Fig. S7: Collins et al. 2022 predicts the haplosensitivity for all autosomal genes referred to as pHaplo score. Bar plot shows a higher median Haplo score than the non-buffered set (TB high; n=187, TB mid; n= 173; Others; n= 11128). n refers to the number of genes

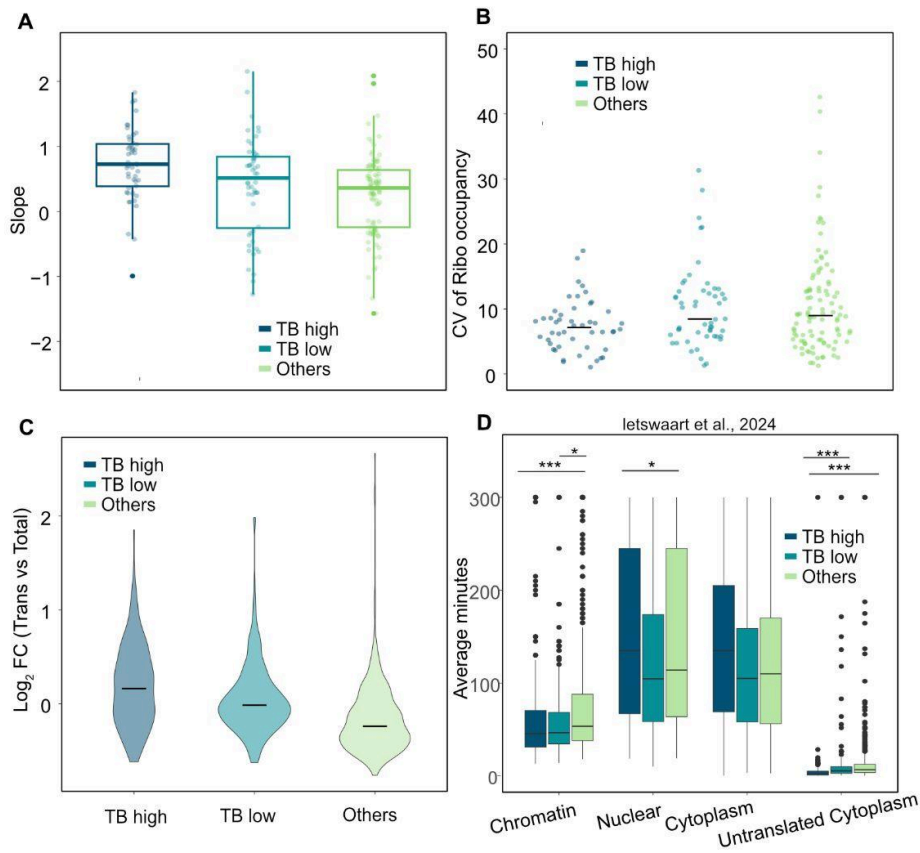


Fig. S8: **A.** Box plot showing the slope between translational RNA and total RNA for the buffered and non-buffered gene set (TB high; n=48, TB low; n= 42; Others; n=100).

non-buffered genes were selected based on their similarity with CV of buffered genes using a matching approach (See Methods) **B.** Sina plot showing the CV of ribosome occupancy levels of the three gene sets from the ribosome profiling experiment carried out in parallel to the RNA-seq of total and translating RNA. Particularly, non-buffered genes were selected based on their similarity with CV of buffered genes using a matching approach (See Methods) (high; n=48, low; n= 52; others; n=100). **C.** Violin plot showing the $\log_2$ fold change between the translational mRNA and total mRNA of genes in three categories (TB high; n=250, TB low; n= 250; Others; n=500). non-buffered genes were selected based on their similarity with expression (cpm values) of buffered genes using a matching approach (See Methods) **D.** Box plot showing the half life measurements of the three categories of gene sets in different compartments including the chromatin, nucleus, untranslated cytoplasm and the cytoplasm wherein the genes in the control set is selected to match the half life of the transcripts in “TB high” and TB low” categories (TB high; n=249, TB low; n= 246; Others; n=495). The half life measurements of mRNA were obtained from [38]. n refers to the number of genes. For visualisation purposes, values greater than 300 have been capped at 300. The p value is after Bonferroni correction. * < 4×10^{-3} , ** < 4×10^{-4} , *** < 4×10^{-5}

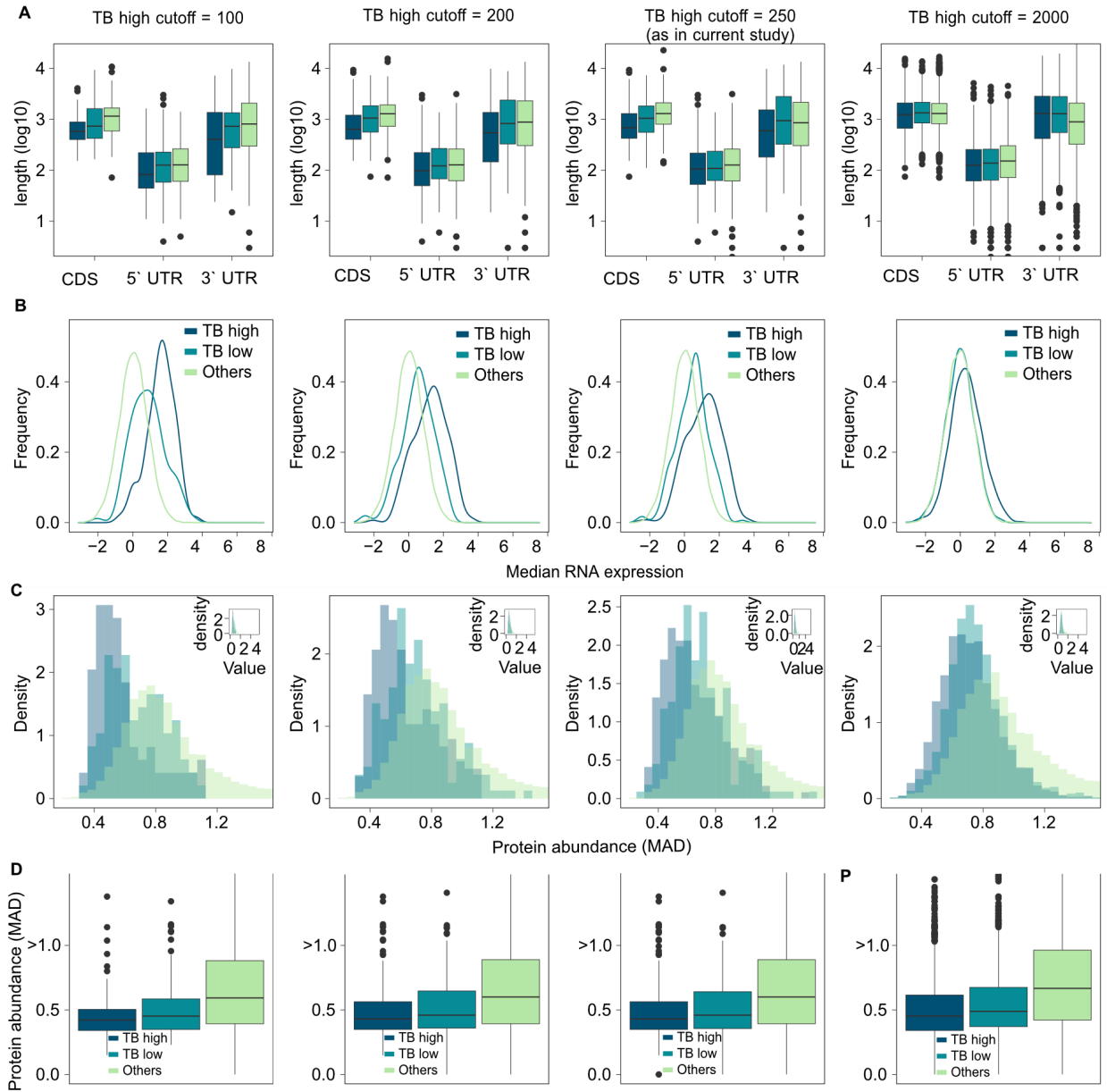


Fig. S9: Effect of different thresholds to define TB high and TB low groups on . A. Length features B. Median RNA expression C. Protein variation in human cancer cell lines and D. on Primary human tissues. The figure shows that the effect on protein variation and association of intrinsic features like the UTR lengths with the buffering potential of genes for different thresholds (i.e. if the TB high = top 100 or TB high = top 200) remain similar to the current cutoff of 250. However, if the cutoff of TB high is increased to 2000 and TB low to top 2000-4000, the difference between the various features is diminished (A& B). Further, protein variation (human cancer cell line and tissue) also becomes more similar across the three categories, possibly indicating a reduced regulatory potential of genes as their rank increases (C& D).

