Figure S1-S10

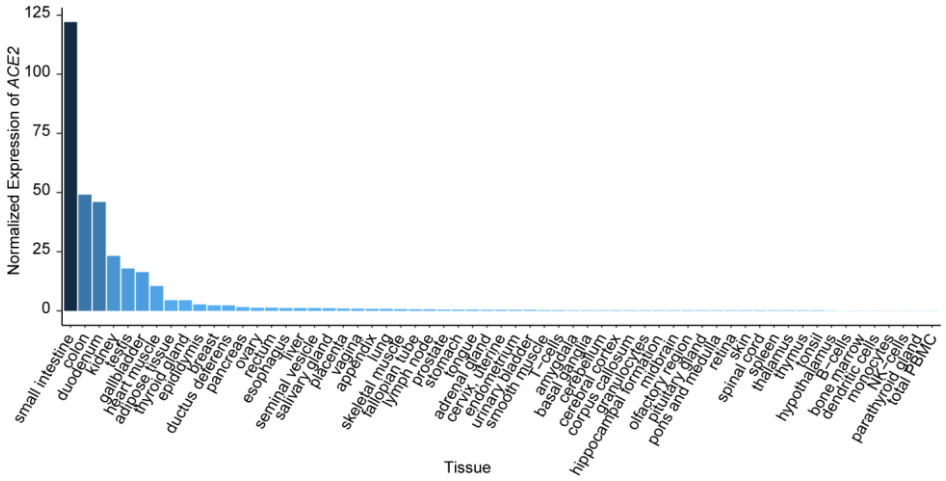

Figure S1 Normalized *ACE2* expression levels in different human tissues. The data used for analysis were retrieved from Human Protein Atlas normalized expression.

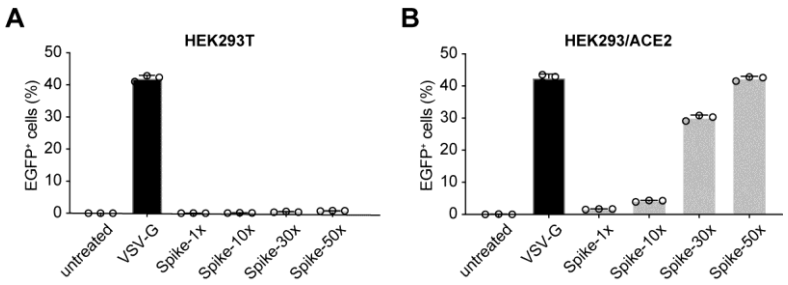

Figure S2 Examination of the approach in simulating SARS-CoV-2 infection using the SARS-CoV-2 pseudotyped virus. A, Examination of the virus infection in wild type HEK293T cells using different concentrations of pseudovirus. HEK293T cells were respectively infected with 1-fold (Spike-1×), 10-fold (Spike-10×), 30-fold (Spike-30×) and 50-fold (Spike-50×) concentrated pseudovirus harboring SARS-CoV-2 S protein, and the $EGFP^+$ percentages were analyzed by FACS 48 h post infection. The lentivirus harboring VSV-G protein was used for infection as a positive control following the same procedure. B, Examination of the concentration of pseudovirus for achieving an efficient virus infection in HEK293 cells stably expressing *ACE2*.

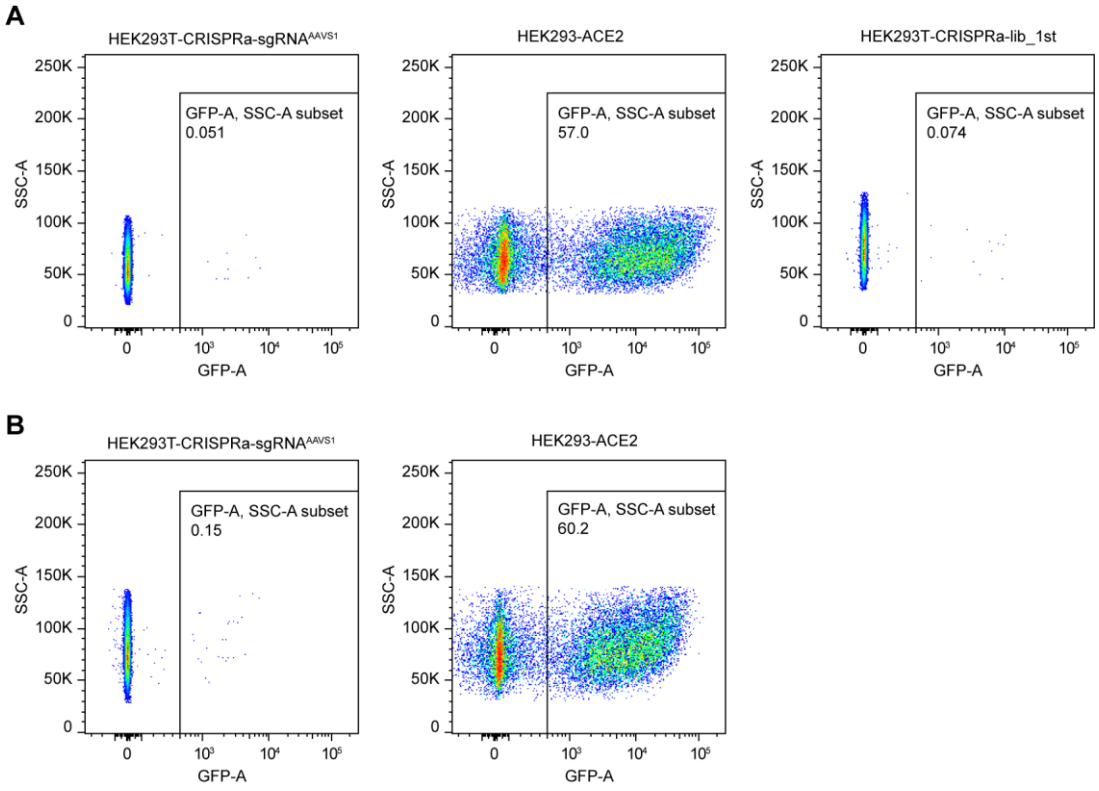

Figure S3 FACS selection of EGFP$^+$ cells in each round of screening after SARS-CoV-2 pseudovirus infection. A, The first FACS selection of EGFP$^+$ cells from the HEK293T-CRISPRa library cells. Left: HEK293T-CRISPRa cells stably expressing *AAVS1*-targeting sgRNA were infected with SARS-CoV-2 pseudovirus (50-fold), serving as the negative control; Middle: HEK293 cells stably expressing ACE2 were infected with SARS-CoV-2 pseudovirus, serving as the positive control; Right: HEK293T-CRISPRa library cells were infected with SARS-CoV-2 pseudovirus for the first round. B, The controls used in the second round of FACS selection of EGFP$^+$ cells. The negative and positive controls were the same as in Figure S3A (left and middle), and the FACS selection of library cells for the second round was presented in Figure 1D.

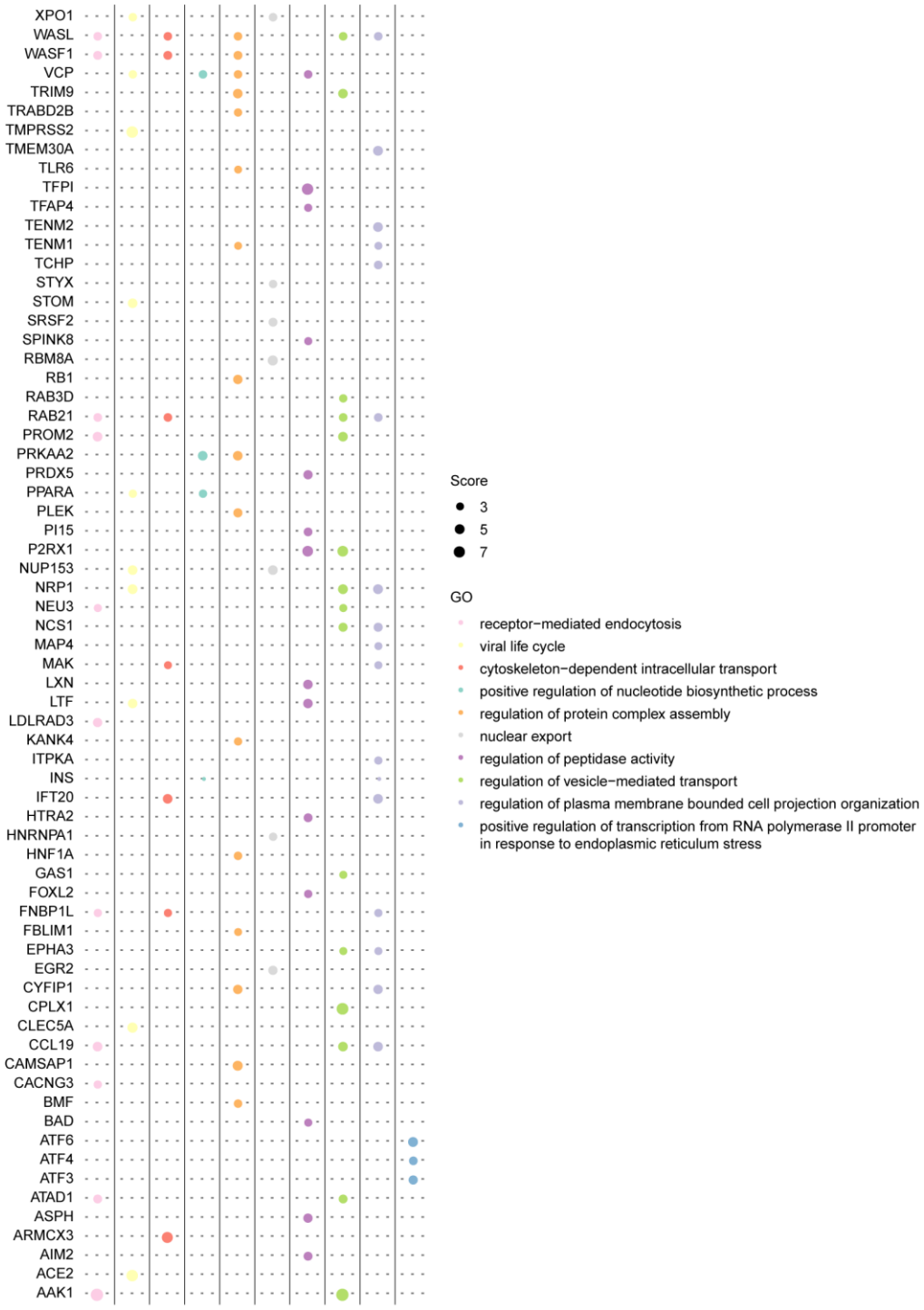

Figure S4 The total gene list from GO enrichment analysis. The size of round dots indicated scores of CRISPRa screening.

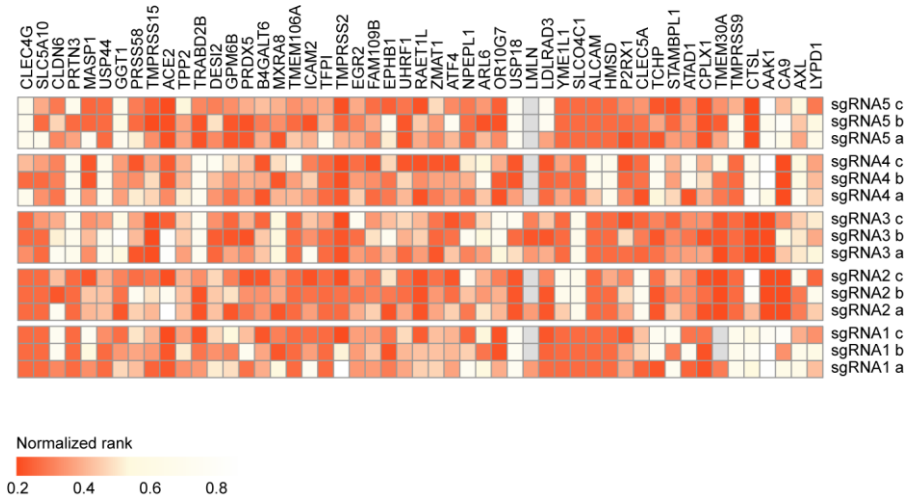

Figure S5 The performance of all the sgRNAs[eBAR] targeting the identified candidates. Three eBARs of each sgRNA were indicated by a, b and c.

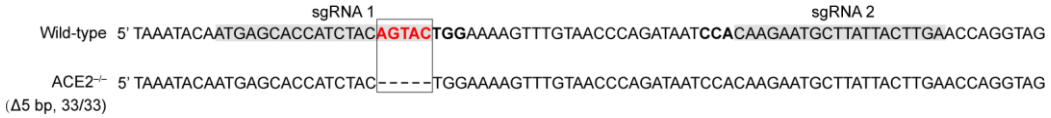

Figure S6 Partial coding sequences of the *ACE2* gene in the genome containing the sgRNA binding regions. The sequencing analysis of the mutated alleles were obtained from 33 randomly selected clones. The dashes indicate deletions.

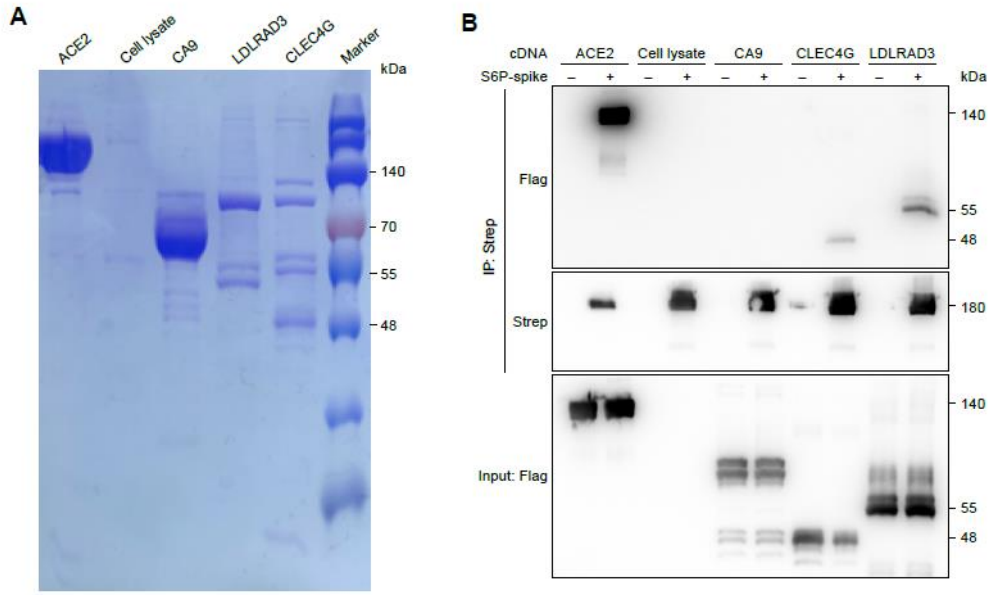

Figure S7 Direct binding of identified proteins to SARS-CoV-2 S. A, Flag-tagged CA9, LDLRAD3, CLEC4G and ACE2 were purified and shown on a Coomassie blue-stained SDS-PAGE gel. B, *In vitro* pull-down assay of purified ACE2, CA9, CLEC4G and LDLRAD3 to SARS-CoV-2 S. Strep-tagged SARS-CoV-2 S and FLAG-tagged candidate receptors were expressed in HEK293T cells and affinity-purified. Immunoblot analysis was conducted using anti-Flag and anti-Strep antibodies.

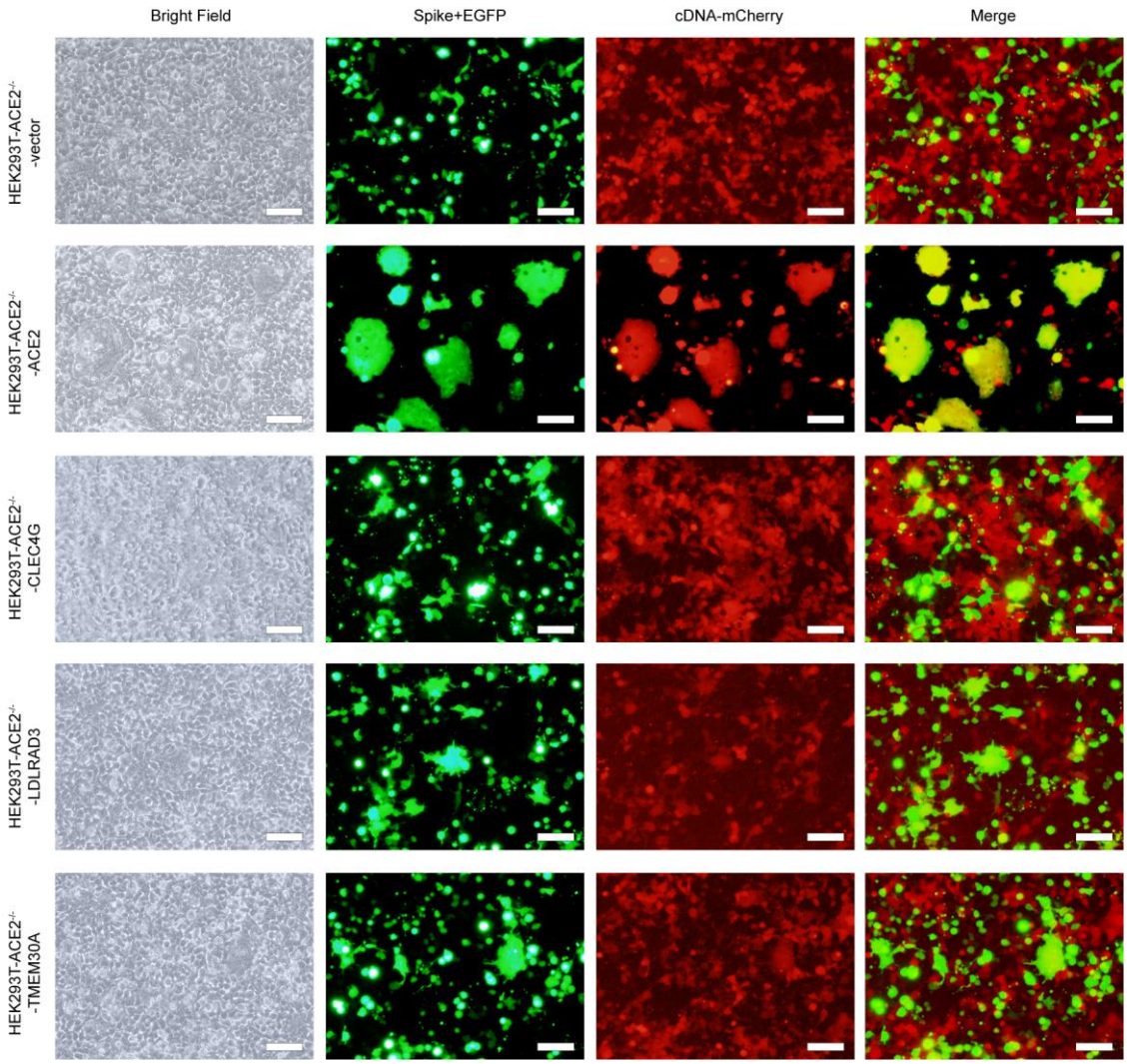

Figure S8 Examination of the interaction between SARS-CoV-2 S protein and candidate receptors in HEK293T *ACE2*$^{-/-}$ cells by syncytium formation assay. The assay was performed following the same procedure as described in Figure 6. The images were taken 40 h after co-culturing the two categories of cells. The scale bar = 100 μm.

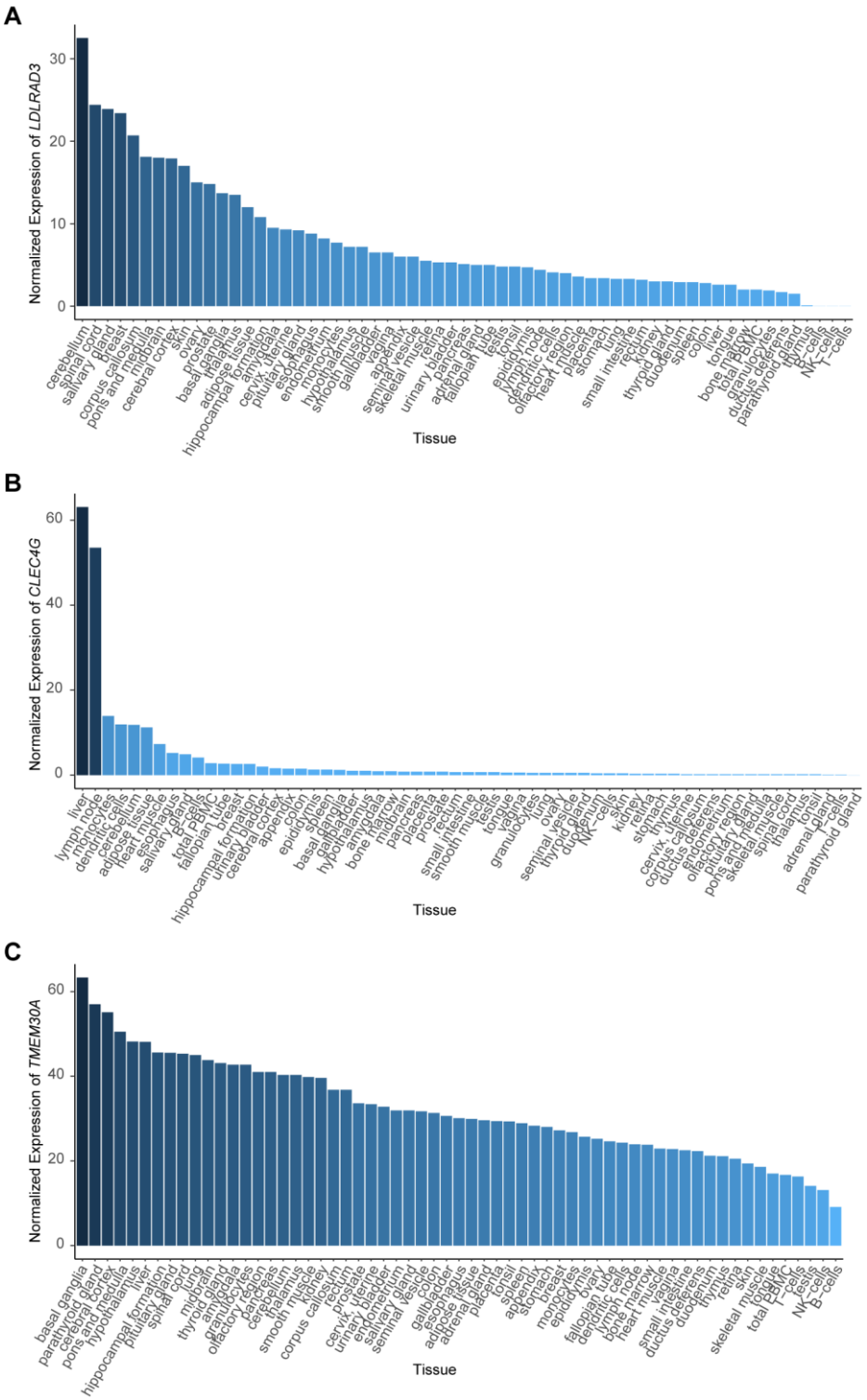

Figure S9 Expression patterns of candidate receptors in human tissues. The mRNA levels of *LDLRAD3* (A), *CLEC4G* (B) and *TMEM30A* (C) within human tissues were analysed using data retrieved from Human Protein Atlas.

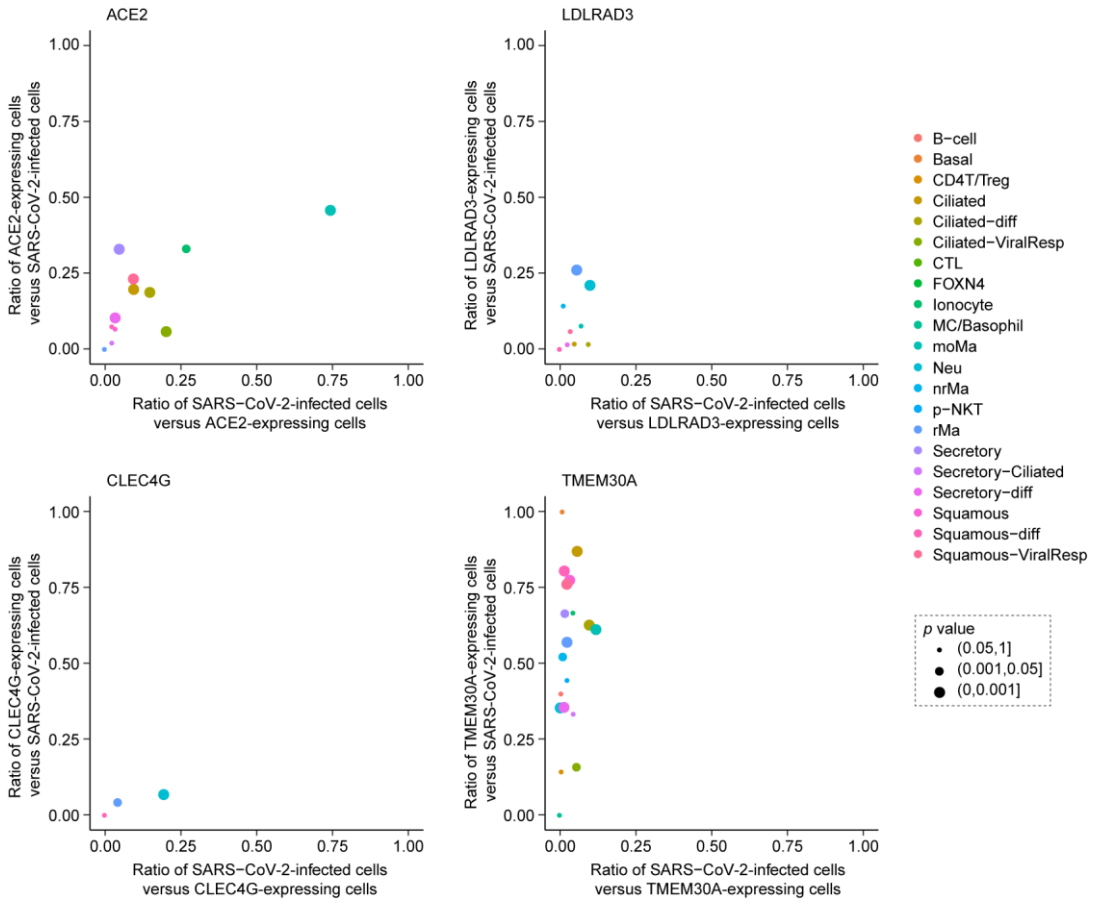

Figure S10 Scatter plots of the co-expression ratios between SARS-CoV-2 and each candidate receptor in different cell types. The x axis represents the ratio of SARS−CoV-2-infected cells versus all cells expressed each candidate receptor. The y axis represents the ratio of cells expressed each candidate receptor versus all SARS−CoV-2-infected cells. The *p* value was calculated by the fisher test to evaluate the significance of co-expression between SARS-CoV-2 and each candidate receptor in each cell type.