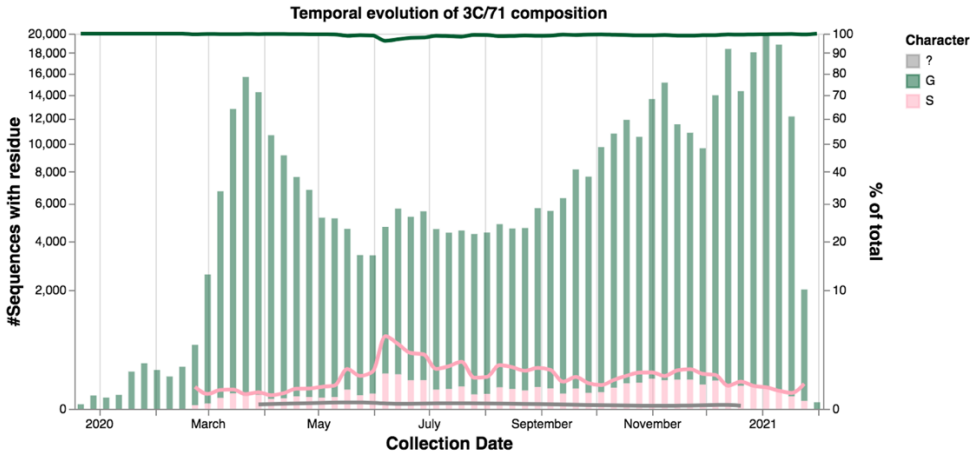
SUPPLEMENTALY FIGURES

A. Temporal distribution of persistent positively SARS-CoV-2 Mpro (3C) selected residues

These analyses were performed using the HyPhy software (1)

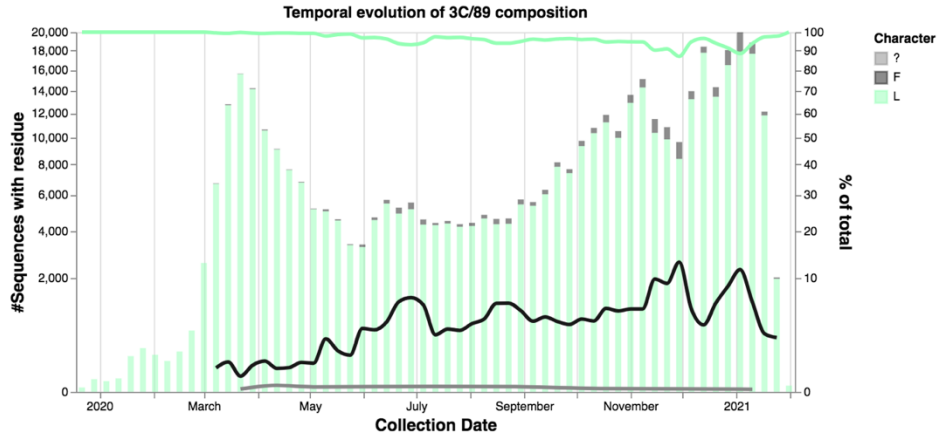
i. G71 in *3C*, genomic coordinate 10265

Residue Frequency: G$_{442884}$S$_{2930}$?$_{10}$



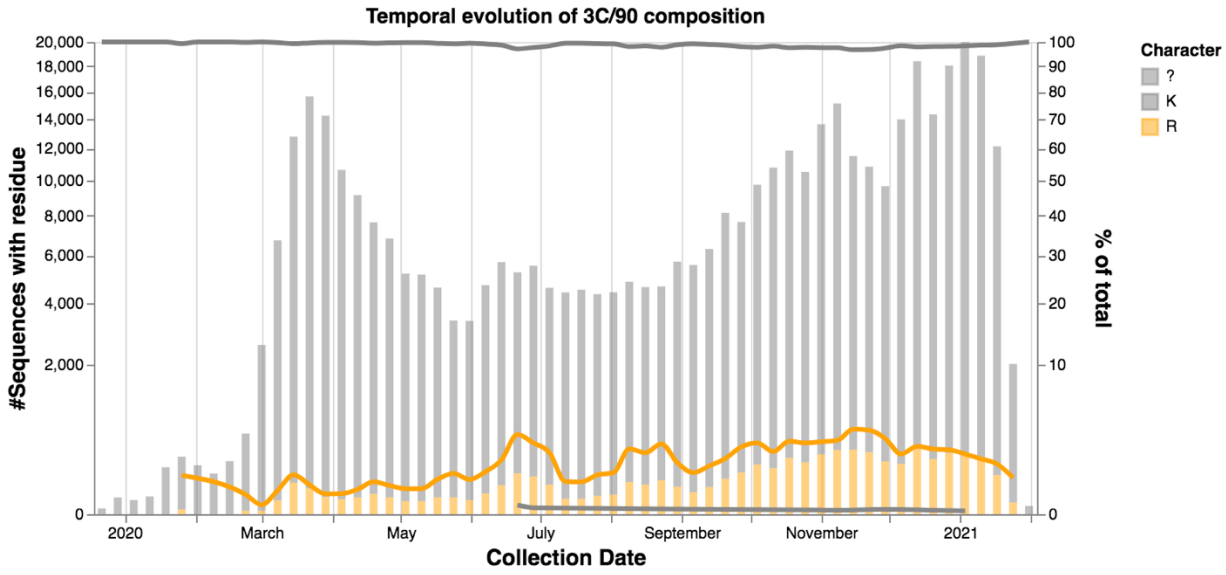
ii. L89 in *3C*, genomic coordinate 10319

Residue Frequency: L$_{426260}$F$_{19555}$?$_{9}$



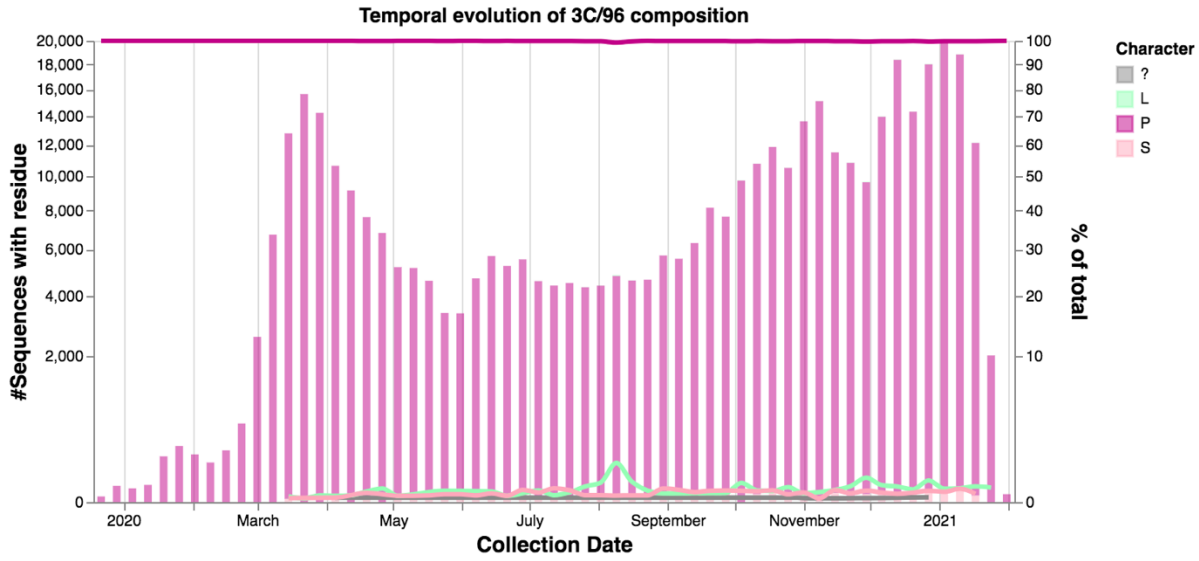
iii. K90 in *3C*, genomic coordinate 10322

Residue Frequency: $K_{439415}R_{6401}?_{8}$

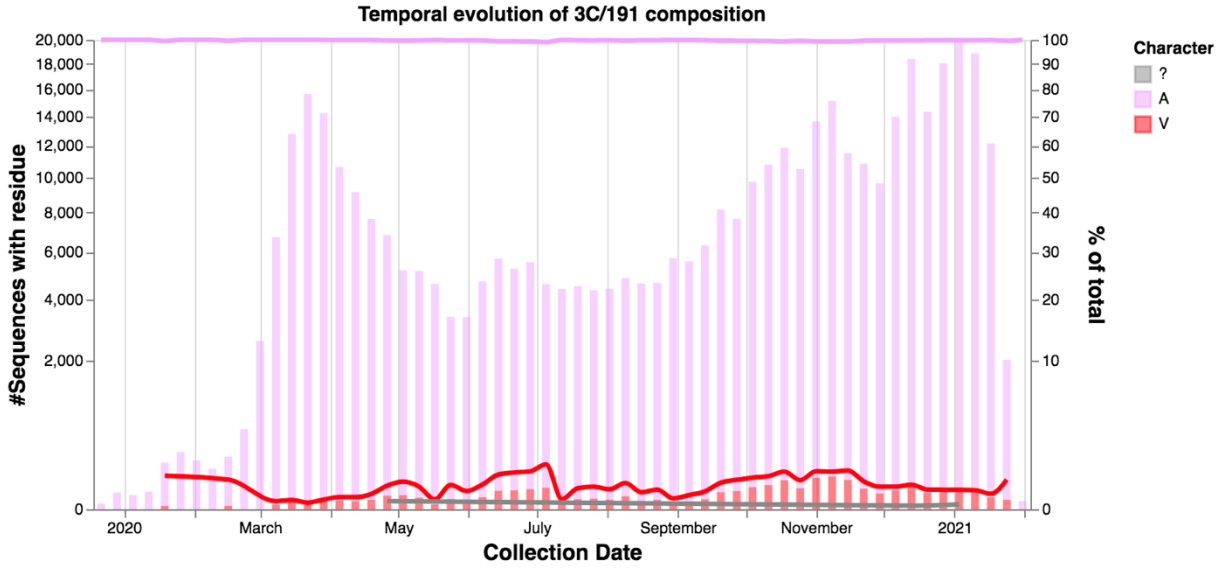


iv. P96 in *3C*, genomic coordinate 10340

Residue Frequency: $P_{445311}L_{351}S_{157}?_{5}$

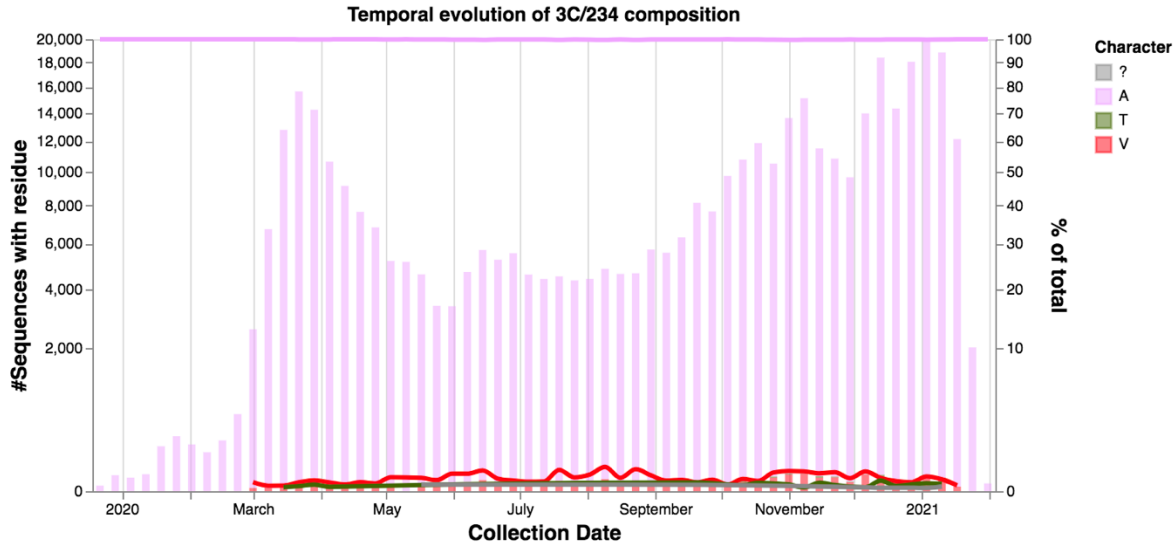


v. A191 in *3C*, genomic coordinate 10625
Residue Frequency: $A_{444656}V_{1163}?_{5}$

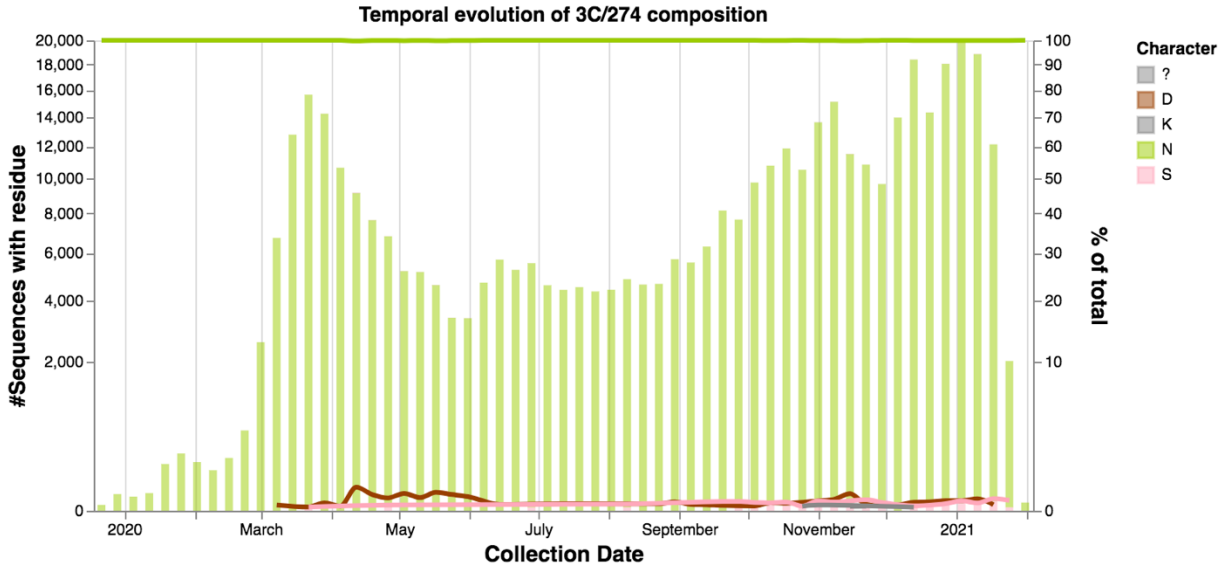


vi. A234 in *3C*, genomic coordinate 10754

Residue Frequency: $A_{445372}V_{384}T_{59}?_{9}$

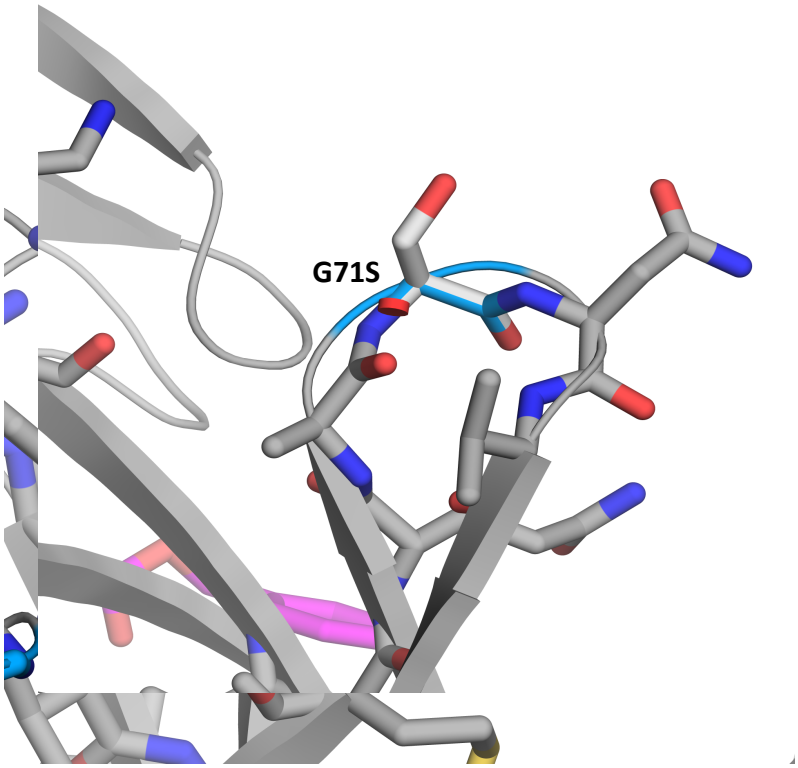


vii. N274 in *3C*, genomic coordinate 10874
Residue Frequency: $N_{445577}D_{165}S_{75}?_5K_2$

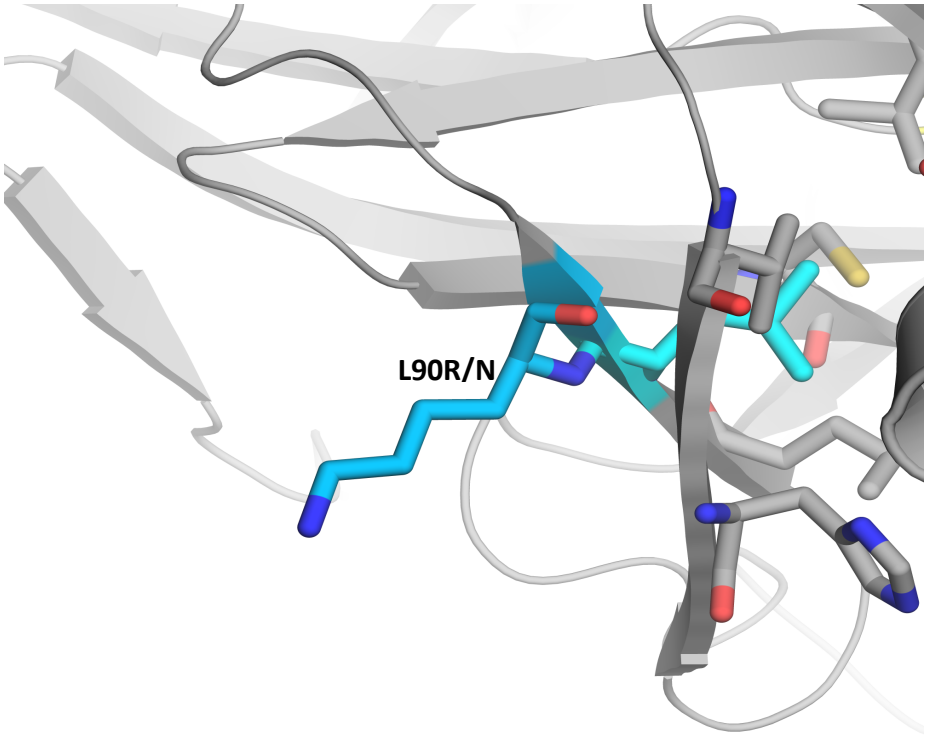


B. Mapping mutations on structure

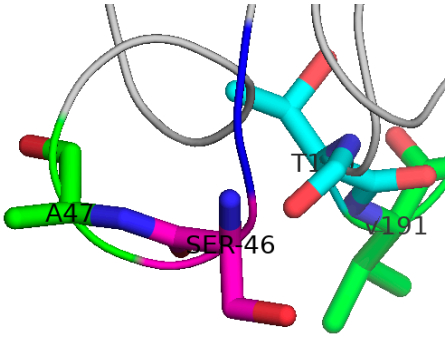
The following figures show the residues and their respective mutants mapped onto SARS-CoV-2 Mpro structure PDB 6LU7 in PYMOL.



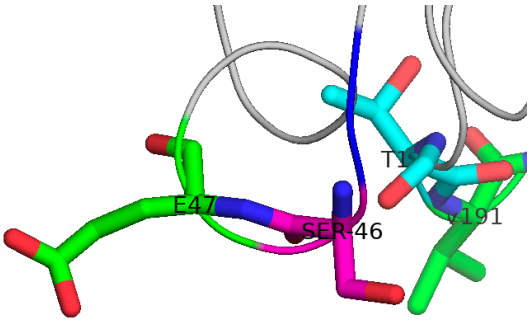
Variant G71S covalently bound to residue S46



Variant L90R/N covalently bound to residue S46



Residue A47 covalently bound to residue S46



Mutant E47 covalently bound to residue S46

References

1. Pond SLK, Frost SDW, Muse SV. HyPhy: hypothesis testing using phylogenies. Bioinformatics. 2005 Mar 1;21(5):676–9.