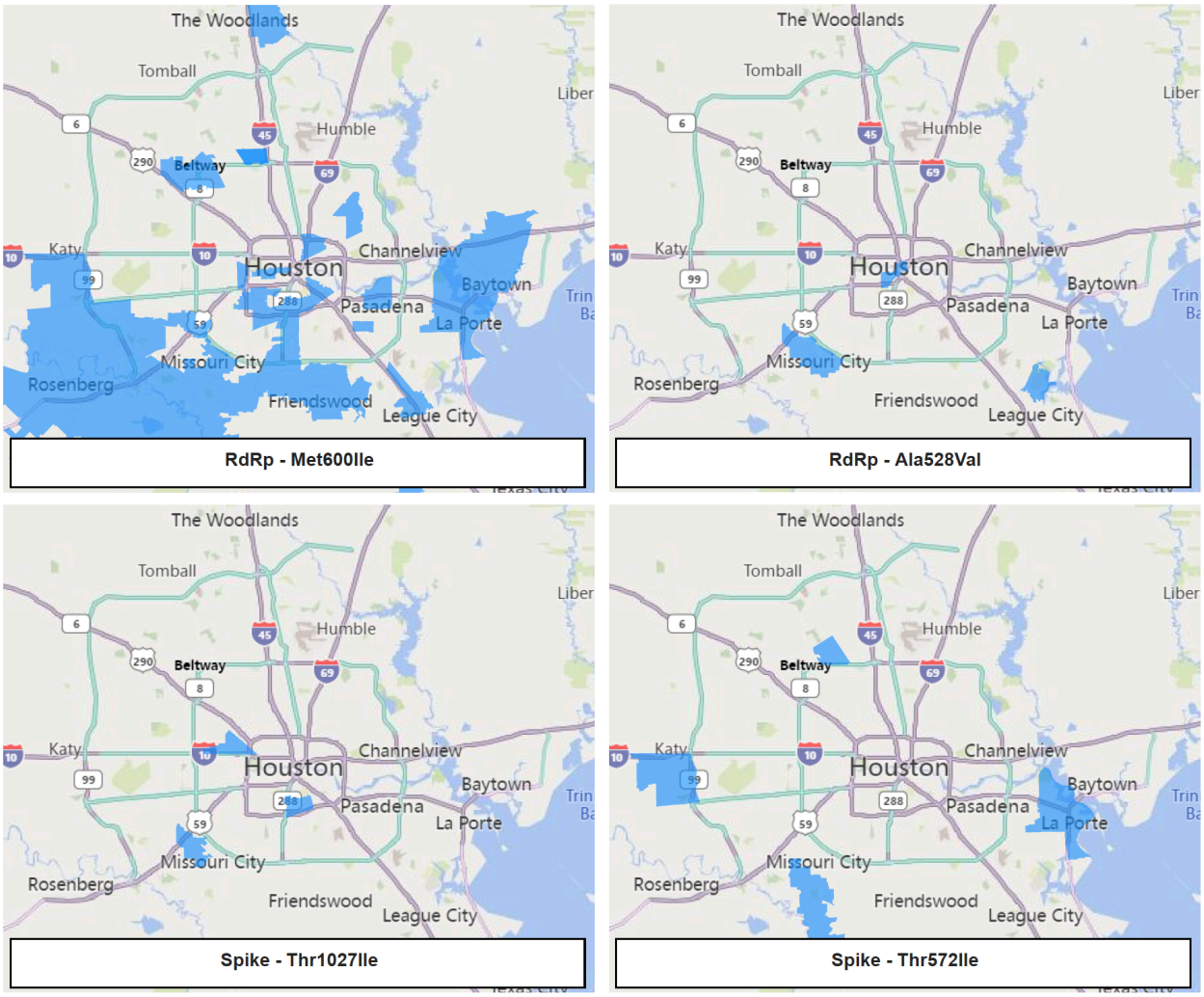
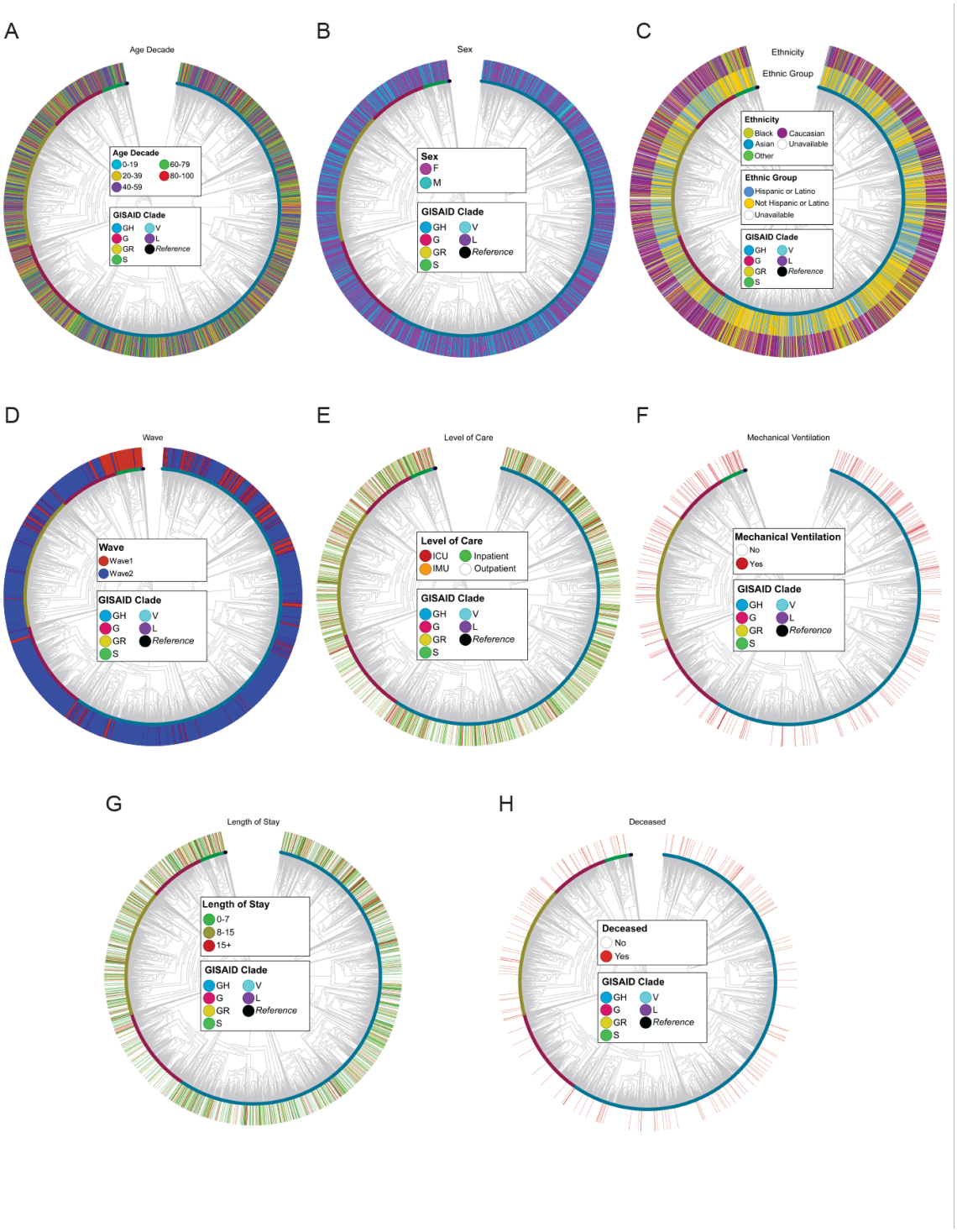
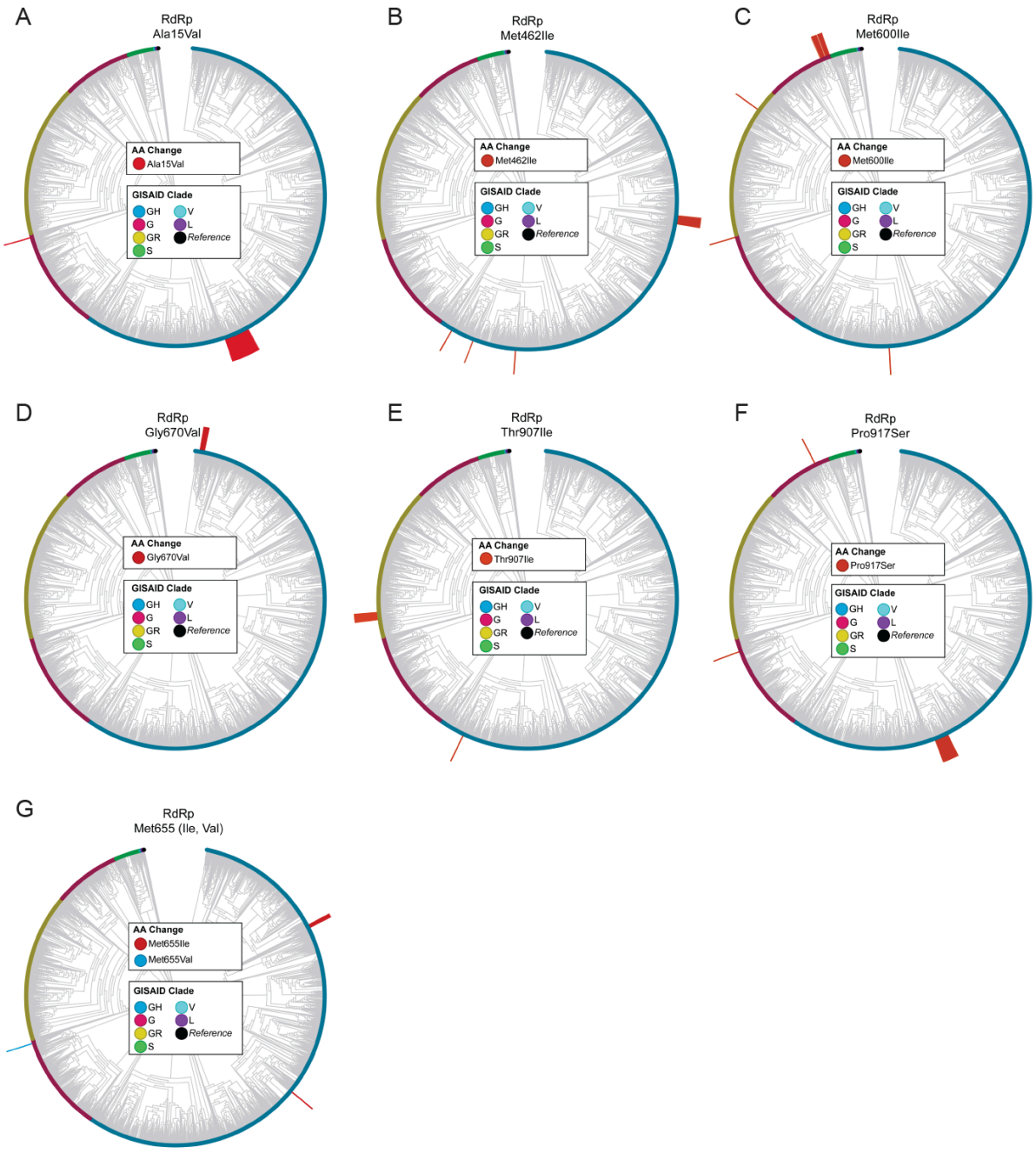


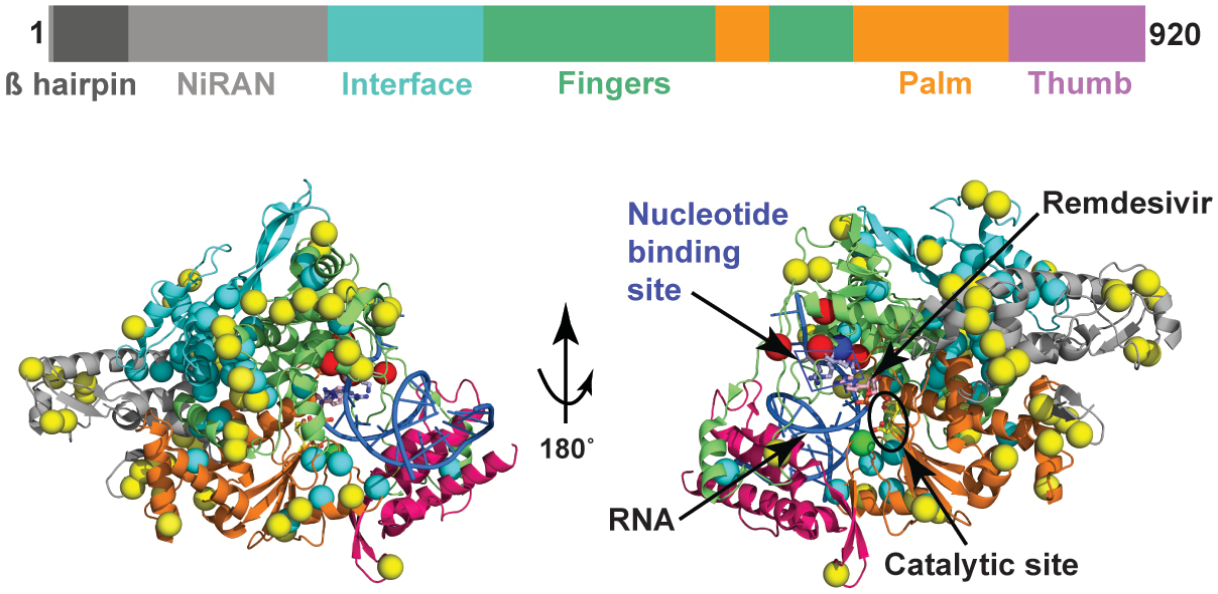
Supplemental FIG 1 Geographic distribution of representative SARS-CoV-2 subclades in the Houston metropolitan region. Blue shaded areas denote zip codes containing COVID-19 cases with the designated subclade.



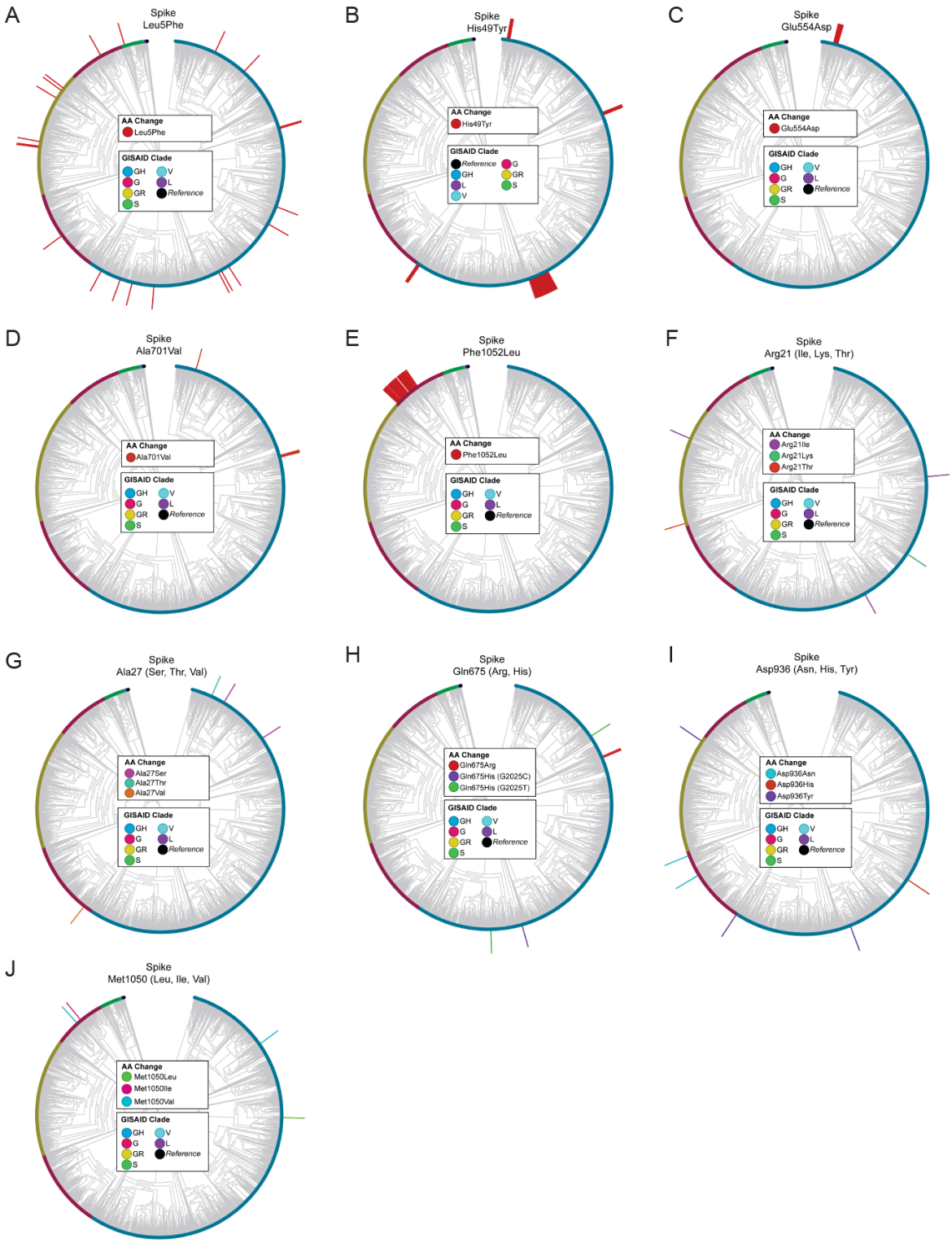
Supplemental FIG 2 Cladograms showing distribution of patient metadata, including (A) age (in decade), (B) sex, (C) ethnicity/ethnic group, (D) wave, (E) level of care, (F) mechanical ventilation, (G) length of stay, and (H) mortality.



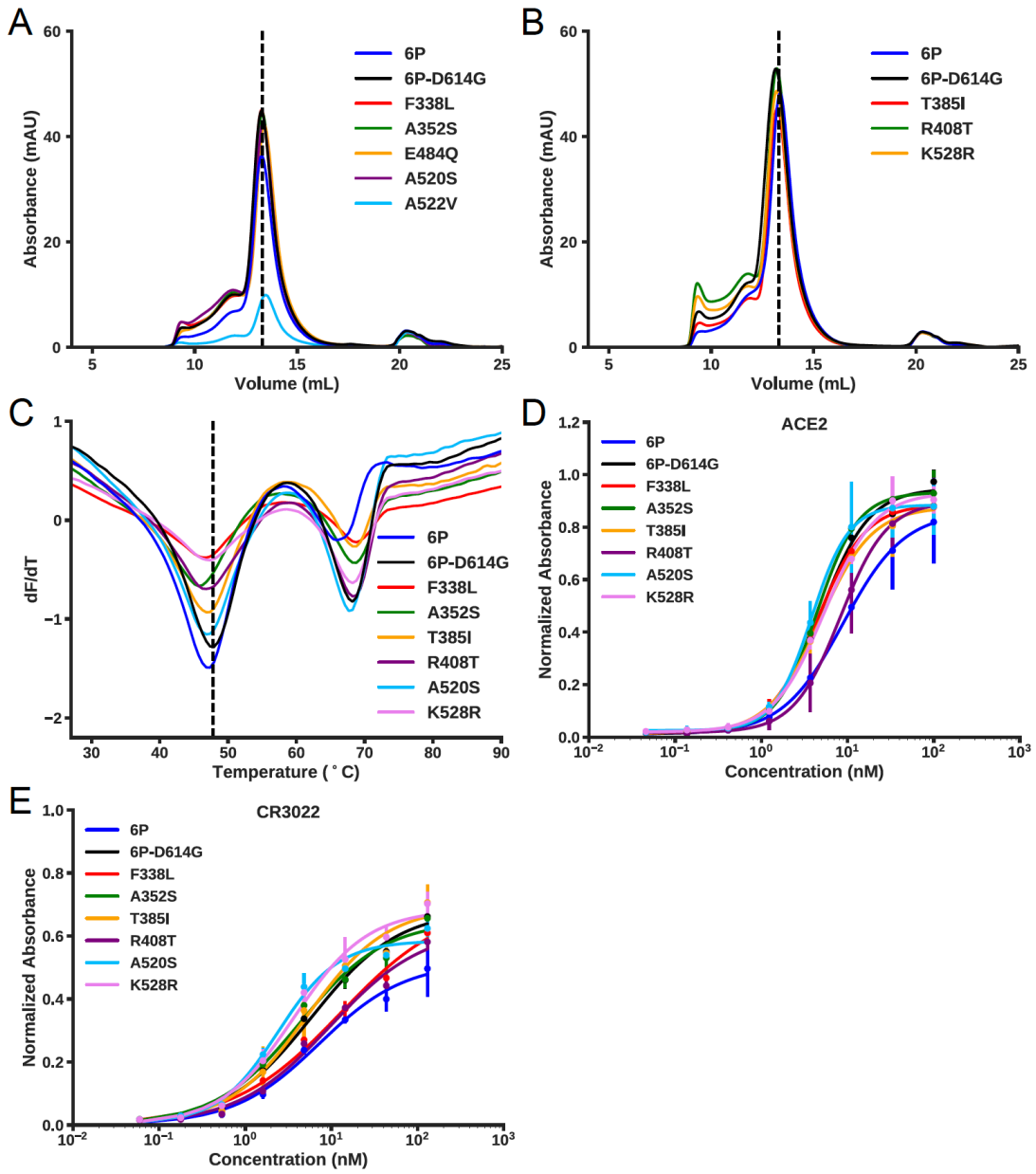
Supplemental FIG 3 Distribution of subclades characterized by particular amino acid replacements in Nsp12 (RdRp).



Supplemental FIG 4 Mapping the location of amino acid replacements on Nsp12 (RdRp) from COVID-19 virus. The schematic on the top shows the domain architecture of Nsp12. The individual domains of Nsp12 are color-coded and labeled. Ribbon representation of the crystal structure of Nsp12-remdesivir monophosphate-RNA complex is shown (PDB code: 7BV2). The structure in the right panel is obtained by rotating the left panel 180˚ along the y-axis. The Nsp12 domains are colored as in the schematic at the top. The positions of Cα atoms of the surface-exposed amino acids identified in this study are shown as yellow spheres, whereas the positions of Cα atoms of the buried amino acids are depicted as cyan spheres. The catalytic site in RdRp is marked by a black circle in the right panel. The side chains of amino acids comprising the catalytic site of RdRp are shown as balls and sticks and colored yellow. The nucleotide binding site is boxed and labeled in the right panel. The side chains of amino acids participating in nucleotide binding (Lys545, Arg553, and Arg555) are shown as balls and sticks. Remdesivir molecule incorporated into the nascent RNA is shown as balls and sticks and colored light pink. The RNA is shown as blue cartoon and bases are shown as sticks. The positions of Cα atoms of amino acids that are predicted to influence remdesivir binding are shown as red spheres. The amino acid Cys812 located at the catalytic site is shown as green sphere. The location of Cα atoms of remdesivir resistance conferring amino acid Val556 is shown as blue sphere and labeled.



Supplemental FIG 5 Distribution of subclades characterized by particular amino acid replacements in spike protein.



Supplemental FIG 6 Biochemical characterization of single amino acid variants of spike protein RBD. (A, B) Size-exclusion chromatography (SEC) traces of the indicated spike-RBD variants. Dashed line indicates the elution peak of spike-6P. (C) Thermostability analysis of RBD variants. Each sample had three replicates and only mean values were plotted. Black vertical dashed line indicates the first melting temperature of 6P-D614G. (D) ELISA-based binding affinities for ACE2 and (E) neutralizing monoclonal antibody CR3022 to the indicated RBD variants.