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Supplementary Material Prediction and mitigation of mutation threats to COVID-19 vaccines and antibody therapies

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S1 Methods

S1.1 Data collection and pre-processing

In this work, we retrieved over 203,246 complete genome sequences with high coverage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains from the infected individuals in the world downloaded from the GISAID database [16] (https://www.gisaid.org/) as of January 20, 2021. The complete genome sequence of SARS-CoV-2 was first released on the GenBank (Access number: NC_045512.2) submitted Zhang's group at Fudan University [24] on January 5, 2020. Since then, there has been a rapid accumulation of SARS-CoV-2 genome sequences. Incomplete records and records without the exact submission date in GISAID were not considered. To rearrange the complete genome sequences according to the reference SARS-CoV-2 genome, multiple sequence alignment (MSA) is carried out by using Clustal Omega [17] with default parameters. The amino acid sequence of NSP2, NSP12, NPS13, spike (S) protein, ORF3a, ORF8, and nucleocapsid were downloaded from the GenBank [1].

S1.2 Sequences, structures and their alignments

All sequences and 3D structures are downloaded from Protein Data Bank (PDB https://www.rcsb.org): sequences are from the FASTA files and 3D structures are from pdb files.

The 3D alignments as well as graphs are created by using PyMOL [5]. The 2D sequence alignments are calculated by clustalw (https://www.genome.jp/tools-bin/clustalw) [20] and 2D alignment graphs are generated by Jalview [23].

S1.3 Secondary structure determination

To guarantee high accuracy, we used a hybrid approach to determine the secondary structure of the S protein. The 3D conformations consisting 1031 of 1273 residues of the S protein are already resolved in PDB structure 7C2L [4], and the secondary structure of these 1031 residues were assigned by PyMOL [5] based on their 3D conformations. The secondary structures of the remaining 242 residues missing in 7C2L were predicted by RaptorX-Property [22].

S1.4 TopNetTree model for protein-protein interaction (PPI) binding free enrrgy changes upon mutation

Mutation-induced protein-protein binding free energy (BFE) changes are an important approach for understanding the impact of mutations on protein-protein interactions (PPIs) and viral infectivity [10]. A variety of advanced methods has been developed [10, 15]. The topology-based network tree (TopNetTree) model [3, 21] is applied to predict mutation-induced BFE changes of PPIs in this work. TopNetTree model was implemented by integrating the topological representation and network tree (NetTree) to predict the BFE changes ($\Delta\Delta G$) of PPIs following mutations [21]. The structural complexity of protein-protein complexes is simplified by algebraic topology [2, 6, 25] and is represented as the vital biological information in terms of topological invariants. NetTree integrates the advantages of convolutional neural networks (CNN) and gradient-boosting trees (GBT), such that CNN is treated as an intermediate model that converts vectorized element- and site-specific persistent homology features into a higher-level abstract feature, and GBT uses the upstream features and other biochemistry features for prediction. The performance test of tenfold cross-validation on the dataset (SKEMPI 2.0 [8]) carried out using gradient boosted regression tree (GBRTs). The errors with the SKEMPI2.0 dataset are 0.85 in terms of Pearson correlation coefficient (R_p) and 1.11 kcal/mol in terms of the root mean square error (RMSE) [21].

S1.4.1 Training set for TopNetTree model

The TopNetTree model is trained by several important training sets. The most important dataset which provides the information for binding free energy changes upon mutations is the SKEMPI 2.0 dataset [8]. The SKEMPI 2.0 is an updated version of the SKEMPI database, which contains new mutations and data from other three databases: AB-Bind [18], PROXiMATE [9], and dbMPIKT [12]. There are 7,085 elements including single- and multi-point mutations in SKEMPI 2.0. 4,169 variants in 319 different protein complexes are filtered as single-pint mutations are used for TopNetTree model training. Moreover, SARS-CoV-2 related datasets are also included to improve the prediction accuracy after a label transformation. They are all deep mutation enrichment ratio data, mutational scanning data of ACE2 binding to the receptor binding domain (RBD) of the S protein [14], mutational scanning data of RBD binding to CTC-445.2 and of CTC-445.2 binding to the RBD [11]. Note the training dataset used in the validation in main text does not include the test dataset, which the mutational data scanning data of RBD binding to CTC-445.2.

S1.4.2 Topology-based feature generation of PPIs

To construct the algebraic topological analysis on protein-protein interactions, we first preset the constructions for a PPI complex into various subsets.

- 1. \mathcal{A}_{m} : atoms of the mutation sites.
- 2. $\mathcal{A}_{mn}(r)$: atoms in the neighbourhood of the mutation site within a cut-off distance r.
- 3. $\mathcal{A}_{Ab}(r)$: antibody atoms within r of the binding site.
- 4. $\mathcal{A}_{Ag}(r)$: antigen atoms within r of the binding site.
- 5. $\mathcal{A}_{ele}(E)$: atoms in the system that has atoms of element type E. The distance matrix is specially designed such that it excludes the interactions between the atoms form the same set. For interactions between atoms a_i and a_j in set \mathcal{A} and/or set \mathcal{B} , the modified distance is defined as

$$D_{\text{mod}}(a_i, a_j) = \begin{cases} \infty, \text{ if } a_i, a_j \in \mathcal{A}, \text{ or } a_i, a_j \in \mathcal{B}, \\ D_e(a_i, a_j), \text{ if } a_i \in \mathcal{A} \text{ and } a_j \in \mathcal{B}, \end{cases}$$
(1)

where $D_e(a_i, a_j)$ is the Euclidian distance between a_i and a_j .

In algebraic topology, molecular atoms of different can be constructed as points presented by $v_0, v_1, v_2, ..., v_k$ as k+1 affinely independent points in simplicial complex. Simplicial complex is a finite collection of sets of points $K = \{\sigma_i\}$, and σ_i are called linear combinations of these points in \mathbb{R}^n $(n \ge k)$. To construct simplicial complex, two that are widely used for point clouds are the Vietoris-Rips (VR) complex and alpha complex which are applied in this model [6]. The boundary operator for a k-simplex would transfer a k-simplex to a k - 1-simplex. Consequently, the algebraic construction to connect a sequence of complexes by boundary maps is called a chain complex

$$\cdots \xrightarrow{\partial_{i+1}} C_i(X) \xrightarrow{\partial_i} C_{i-1}(X) \xrightarrow{\partial_{i-1}} \cdots \xrightarrow{\partial_2} C_1(X) \xrightarrow{\partial_1} C_0(X) \xrightarrow{\partial_0} 0$$

and the kth homology group is the quotient group defined by

$$H_k = Z_k / B_k. \tag{2}$$

Then the Betti numbers are defined by the ranks of kth homology group H_k which counts k-dimensional invariants, especially, $\beta_0 = \operatorname{rank}(H_0)$ reflects the number of connected components, $\beta_1 = \operatorname{rank}(H_1)$ reflects the number of loops, and $\beta_2 = \operatorname{rank}(H_2)$ reveals the number of voids or cavities. Together, the set of Betti numbers $\{\beta_0, \beta_1, \beta_2, \cdots\}$ indicates the intrinsic topological property of a system.

Persistent homology is devised track the multiscale topological information over different scales along a filtration [6] and is significant important for constructing feature vectors for the machine learning method. Features generated by binned barcode vectorization can reflect the strength of atom bonds, van der Waals interactions, and can be easily incorporated into a CNN, which captures and discriminates local patterns. Another method of vectorization is to get the statistics of bar lengths, birth values, and death values, such as sum, maximum, minimum, mean, and standard derivation. This method is applied to vectorize Betti-1 (H_1) and Betti-2 (H_2) barcodes obtained from alpha complex filtration based on the facts that higher-dimensional barcodes are sparser than H_0 barcodes.

S1.4.3 Machine learning models

It is very challenging to predict binding affinity changes following mutation for PPIs due to the complex dataset and 3D structures. A hybrid machine learning algorithm that integrates a CNN and GBT is designed to overcome difficulties, such that partial topologically simplified descriptions are converted into concise features by the CNN module and a GBT module is trained on the whole feature set for a robust predictor with effective control of overfitting [21]. The gradient boosting tree (GBT) method produces a prediction model as an ensemble method which is a class of machine learning algorithms. It builds a popular module for regression and classification problems from weak learners. By the assumption that the individual learners are likely to make different mistakes, the method using a summation of the weak learners to eliminate the overall error. Furthermore, a decision tree is added to the ensemble depending on the current prediction error on the training dataset. Therefore, this method (a topology-based GBT or TopGBT) is relatively robust against hyperparameter tuning and overfitting, especially for a moderate number of features. The GBT is shown for its robustness against overfitting, good performance for moderately small data sizes, and model interpretability. The current work uses the package provided by scikit-learn (v 0.23.0) [13]. A supervised CNN model with the PPI $\Delta\Delta G$ as labels is trained for extracting high-level features from H_0 barcodes. Once the model is set up, the flatten layer neural outputs of CNN are feed into a GBT model to rank their importance. Based on the importance, and ordered subset of CNN-trained features is combined with features constructed from high-dimensional topological barcodes, H_1 and H_2 into the final GBT model.

S2 Multiple sequence alignments of antibodies and pairwise identity scores

Through the sequence clustering algorithm in CD-HIT suite [7], the 46 antibodies were classified into 28 clusters. Among them, the first five clusters contain more than one antibody. Figures S1-S5 are the multiple sequence alignments of these five clusters. The pairwise identity scores inside each of these five clusters are over 0.9, especially clusters 2 and 4 have such scores over 0.95. Their pairwise identity scores are deposited in the file "antibody-2d-score-matrix.csv".

BD-236 1 - EVOLVESGGGLIOPGGSLELSCAASGITVSSNYMSWVROAPGKGLEWVSVIYSG6-STDYADSVKGRFTISROKSKNTLYLOMNSLRAEL BD-604 1 - EVOLVESGGGLIOPGGSLELSCAASGIVSSNYMSWVROAPGKGLEWVSVIYSG6-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL C1A 1 - EVOLVESGGGLIOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVIYSG6-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL A_Fab 1 - EVOLVESGGGVOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVIYSG6-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S304 1 - EVOLVESGGGLOPGGSLELSCAASGFTFSSYDMHWVROAPGKGLEWVSVIYSG6-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S304 1 - VOLVESGGGLOPGGSLELSCAASGFTFSSYDMHWVROAPGKGLEWVSVIYSG6-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTFSSYDMHWVROAPGKGLEWVSTIGTAG-DTYPDSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTFSSYDMHWVROAPGKGLEWVSTISTGTAG-DTYPDSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTFSSYDMHWVROAPGKGLEWVSTISTGTAG-DTYPDSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTFSSYDMMWVROAPGKGLEWVSVISTISGG-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVISTISGG-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVISTISGG-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S204 1 - EVOLVESGGGLOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVISTSGG-STFYADSVKGRFTISRONSKNTLYLOMNSLRAEL S205 1 - EVOLVESGGGLOPGGSLELSCAASGFTVSSNYMSWVROAPGKGLEWVSVISTSG	DTAVYYC 95 DTAVYYC 95 DTAVYYC 96 DTAVYYC 94 DTAVYYC 96 DTAVYYC 96 DTAVYYC 95 DTAVYYC 95 DTAVYYC 95 DTAVYYC 97 DTAVYYC 95
BD-236 96 AR DLGEAGGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI BD-604 96 AR -DLGPYG-MDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI C1A 96 ARGDVSGYRYGLDVWGQGTLVTVSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI C1A 96 ARGDVSGYRYGLDVWGQGTLVTVSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S4_Fab 96 AR - DLQELGSLDVWQQGTLVTVSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S304 95 ARGDSSGVMYYFDVWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S304 97 ARGDSSGVMYYFDVWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S204 97 ARGDSSGVMYYFDVWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S204 97 ARGDSGTUVYSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S205 97 ARDFLDWYGLDVWQQGTTVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S215 97 ARDFLDWYGLDVWQQGTTVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S215 97 ARDLDWYGLDVWQQGTWVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSI S215	SVVTVPS 190 SVVTVPS 193 SVVTVPS 191 SVVTVPS 192 SVVTVPS 192 SVVTVPS 190 SVVTVPS 191 SVVTVPS 192 SVVTVPS 190 SVVTVPS 190 SVVTVPS 190 SVVTVPS 190 SVVTVPS 190 SVVTVPS 190 SVVTVPS 192
BD-236 192 SSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKAIQLTQSPSSLSASVGDRVTITCRASQGIS SYLAWYQQKPGKAPKLLIY BD-604 191 SSLGTQTYICNVNHKPSNTKVDKKVEPKS CDRDUCICQSPSFLSASVGDRVTITCRASQGIS SDLAWYQQKPGKAPKLLIY C1A 194 SSLGTQTYICNVNHKPSNTKVDKKVEPKS CDRDUCICQSPSFLSASVGDRVTITCRASQGIS SDLAWYQQKPGKAPKLLIY A_Fab 192 SSLGTVTCNVNHKPSNTKVDKKVEPKS CDRDUCICQSPSSVSASVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY A_Fab 192 SSLGTQTYICNVNHKPSNTKVDKKVEPKS CPCP PCPIOIQMTQSPSSVSASVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY EY6A 195 SSLGTQTYICNVNHKPSNTKVDKKVEPKS CPCP PCPIOIQMTQSPSSVSASVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY 2304 193 SSLGTQTYICNVNHKPSNTKVDKKVEPK CCPCP CPCPIOIQMTQSPSSVSASVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY 220:13 193 SSLGTQTYICNVNHKPSNTKVDKKVEPK CCPCPI CCRASSVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY 27:143 193 SSLGTQTYICNVNHKPSNTKVDKKVEPK CCPCPI CCRASSVGDRVTITCRASQGIS SVLAWYQQKPGKAPKLLIY 27:191 SSLGTQTYICNVNHKPSNTKVDKKVEPKSCAAAH SSLGTQTYICNVNHKPSNTKVDKKVEPKSCAAAH SSLGTQTYICRVPKSCAAAH SSLGTQTYICRVPKSCAAAH SSLGTQTYICRVPKSKQGRVTITCRASQGIS	AASTLQS 278 AASTLQS 281 AASSLQS 282 AASSLQS 282 AASTLQS 278 AASTLQS 278 AASTLQS 274 AASTLQS 276 AASTLQS 276 AASTLQS 280 AASTLQS 280 AASTLQS 289
BD-236 280 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQLN SUPPAFGGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA BD-604 279 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQLN SDLYT FGGGT KLEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA A 282 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQLN SDLYT FGGGT KLEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA A_Fab 285 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQLN SFPT FGGT KLEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA EY64 283 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQSY SFPT FGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA S304 279 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQSY STLALT FGGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA P2C-1A3 275 GVP SR FSGSGSGTD FT LT ISSLOPED FATYYCOQLN SYPLT FGGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA P2C-112 277 GVP SR FSGSGSGT EFT LT ISSLOPED FATYYCOQLN SYPLT FGGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA P2C-112 277 GVP SR FSGSGSGT EFT LT ISSLOPED FATYYCOQLN SYPLT FGGGT KVEIKRTVAAP SVFIFPP SDEQLKSGT ASVVCLLNNFYPREA CC12.1 277 GVP SR FSGSGSGT EFT LT ISSLOPED FATYYCOQLN SYPLT FGGGT KVEIKRTVAAP SVFIFP SDEQLKSGT ASVVCLLNNFYPREA C213 275 SVP SR FSGSGSGT EFT LT ISSLOPED FATYYCOQLN SYPLT FGGGT KVEIKRTVAAP SVFIFP SDEQLKSGT ASVVCLLNNFYPREA C2141 277 GVP SR FSGSG	KVQWKVD 373 KVQWKVD 376 KVQWKVD 379 KVQWKVD 378 KVQWKVD 374 KVQWKVD 369 KVQWKVD 373 KVQWKVD 373 KVQWKVD 373 KVQWKVD 373 KVQWKVD 376 KVQWKVD 376 KVQWKVD 376
BD-236375NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -BD-604374NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -C1A377NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -A_Fab380NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S304375NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S20-413370NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S20-413370NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S20-413370NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S21-413370NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -S259-C113381NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -B38377NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -B38377NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC -B38377NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC SC0VA2-04379NALOSGNSGESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC S	437 436 439 442 441 437 432 437 443 440 450 441

Figure S1: The 2D sequence alignment of the antibodies in cluster 1: BD-236, BD-604, C1A, a fab, EY6A, S304, P2C-1A3, CC12.1, STE90-C11, B38, CB6, COVA2-04.

CV30 1 QVQLVESGGGLIQPGGSLRLSCAASGVIVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSL P2C-1F11 1 EVQLVESGGGLVQPGGSLRLSCAASGITVSSNYMNWVRQAPGKGLEWVSLIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLR BD-629 1 EVQLVESGGGLIQPGGSLRLSCAASGFVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLNLQMNSLR CC12.3 1 QVQLVESGGGLIQPGGSLRLSCAASGFVSSNYMSWVRQAPGKGLEWVSVIYSGGSTFYADSVKGRFTISRDNSKNTLNLQMNSLR	AEDTAVYHC 95 AEDTAVYYC 95
CV30 96 A RDLDVSGGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY P2C-1F11 96 A RDLVVYG-MDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY BD-629 96 A RDYGDYY-FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY CC12.3 96 A RDFGDFY-FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY	SLSSVVTVP 189
CV30 191 SSSLGTOTYICNVNHKPSNTKVDKKVEPKSCDKTQIVLTOSPGTLSLSPGERATLSCRASOSVSSSYLAWYOOKPGOAPRLLIYGA P2C-1F11 190 SSSLGTOTYICNVNHKPSNTKVDKKVEPEIVLTOSPGTLSLSPGERATLSCRASOSVSSSYLAWYOOKPGOAPRLLIYGA BD-629 190 SSSLGTOTYICNVNHKPSNTKVDKKVEPKSC-DKEIVLTOSPGTLSLSPGERATLSCRASOGVSS-FLAWYOOKPGOAPRLLIHGA CC12.3 190 SSSLGTOTYICNVNHKPSNTKVDKKVEPKSCEIVLTOSPGTLSLSPGERATLSCRASOSVSS-YLAWYOOKPGOAPRLLIYGA	ASS <mark>R</mark> ATGIPD 278 ASS <mark>R</mark> ATGIPD 282
CV30 286 RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPQTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV P2C-1F11 279 RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSP-TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV BD-629 283 RFSGSGSGTDFTLTITRLEPEDFAVYYCQQYGSSPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV CC12.3 281 RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV	/QW <mark>K</mark> VDNALQ 372 /QWKVDNALQ 377
CV30 381 SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC - P2C-1F11 373 SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC - BD-629 378 SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC - CC12.3 376 SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC S	439 431 436 435

Figure S2: The 2D sequence alignment of the antibodies in cluster 2: CV30, P2C-1F11, BD-629, CC12.3.

COVA2-39 CV07-270		(YC 95 (YC 96
COVA2-39	9 96 A <mark>R</mark> AHVDTAMVESGAFDIWGOGTRVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS	3LY 186
CV07-270	9 97 A <mark>R</mark> ARGSSGWYRIGTRWGNWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS	3LY 192
COVA2-39 CV07-270	9 187 <mark>SLSSVVTVPSSSLGTQTYICNVNHKPSNTK</mark> VDKRVEPKSCHHHHHHQSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK 9 193 <mark>SLSSVVTVPSSSLGTQTYICNVNHKPSNTK</mark> VDK <mark>K</mark> VEPKSCQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPK	MI 282
COVA2-39	9 283 YEVTK <mark>RPSGVSNR</mark> FSGSKSGNTASLT I SGLQAEDEADYYCCSYA <mark>GSS</mark> TWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCL I SDF	<mark>(PG</mark> 378
CV07-270	9 283 YEVSN <mark>RPSGVSNR</mark> FSGSKSGNTASLT I SGLQAEDEADYYCSSYTSSSNVVFGGGTMLTVLGQPKAAPSVTLFPPSSEELQANKATLVCL I SDF	(PG 378
COVA2-39	9 379 AVTVAWKADSSPVKAGVETTTPSKOSNNKYAASSYLSLTPEOWKSHRSYSCOVTHEGSTVEKTVAPTECS	448
CV07-270	9 379 AVTVAWKADSSPVKAGVETTTPSKOSNNKYAASSYLSLTPEOWKSHRSYSCOVTHEGSTVEKTVAPTECS	448

Figure S3: The 2D sequence alignment of the antibodies in cluster 3: COVA2-39, CV07-270.

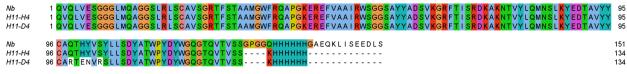
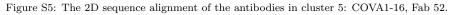


Figure S4: The 2D sequence alignment of the antibodies in cluster 4: Nb, H11-H4, H11-D4.





S3 Random coil percentages of antibody paratopes

Table S1 depicts the random coil percentages of antibody paratopes on S protein, which indicates antibodies predominantly contact residues in random coils of the S protein.

S4 Additional analysis of antibody-S protein complexes

Three antibodies, i.e., 4A8, FC05, and 2G12, do not bind to the RBD. Among them, 4A8 has been analyzed in the main text of the paper and 2G12 involves small molecules at its binding site with the S2 domain of the S protein, which cannot be handled by the present model. Antibody FC05 has two complexes with the S protein (i.e., 7CWU and 7CDJ). Both of them share the same antibody at the N-terminal domain (NTD).

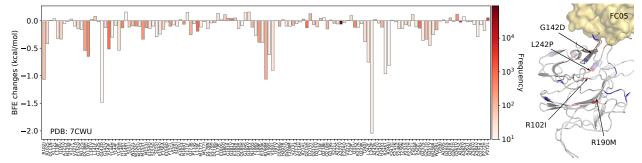


Figure S6: Illustration of SARS-CoV-2 mutation-induced binding free energy changes for the complexes of S protein and FC05 (PDB: 7CWU). Blue color in the structure plot indicates a positive BFE change while red color indicates a negative BFE change, and toning indicates the strength. Here, mutations R102I, G142D, R190M, and L242P could potentially disrupt the binding of antibody FC05 and the S protein.

Figure S6 illustrates the common binding complex of FC05 with the S protein NTD. A total 131 out of 501 mutations on residues ID from 14 to 226 have their frequencies larger than 10. Only 13 of these 131 mutations have their magnitudes of BFE changes large than 0.5 kcal/mol. In particular, the largest magnitude of binding-strengthening mutation has a BFE change of 0.16 kcal/mol. Moreover, 99 out of the 131 mutations have negative BFE changes, including R102I with the frequency of 89.

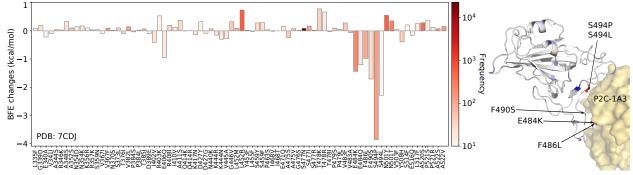


Figure S7: Illustration of SARS-CoV-2 mutation-induced binding free energy changes for the complexes of S protein and P2C-1A3 (PDB: 7CDJ). Blue color in the structure plot indicates a positive BFE change while red color indicates a negative BFE change, and toning indicates the strength. Here, mutations E383K, F486L, F490S, S494P, and S494L could potentially disrupt the binding of antibody P2C-1A3 and the S protein.

We also present in a detailed study of antibody P2C-1A3 because it can be disrupted by a relatively high frequency mutation S494P with a large negative BFE change. Figure S7 illustrates the mutation-induced BFE changes for antibody P2C-1A3 (PDB: 7CDJ), which also shares the binding domain with ACE2. Note that mutation S494P has a BFE change of -3.9 kcal/mol with a frequency of 123. This antibody has mild BFE changes outside the binding motif but dramatic negative changes at mutations on the binding motif.

Antibody	The number of residues	The number of random-coil	Percentage
	inside the paratope	residues inside the paratope	
BD-629	27	25	92.6 %
CB6	34	31	91.8~%
COVA2-04	32	31	96.9~%
CV30	29	28	96.6~%
CC12.1	38	36	94.7 %
CC12.3	26	25	96.2~%
BD-236	33	31	93.9~%
BD-368-2	18	17	94.4 %
BD-604	33	31	93.9~%
H11-H4	18	17	94.4 %
H11-D4	18	18	100.0 %
COVA2-39	17	17	100.0 %
H014	26	20	76.9 %
P2B-2F6	19	18	94.7 %
SR4	21	21	100.0 %
BD23	19	18	94.7 %
S309	21	10	81.0 %
CR3022	28	23	82.1 %
B38	34	32	94.1 %
Fab2-4	17	17	100.0 %
MR17	20	20	100.0%
EY6A	20	20	85.2 %
Nb	17	16	94.1 %
S2H13			94.1% 100.0 %
	13	13	
S2A4	19	18	94.7 %
S304	12	12	100.0 %
VH binder	26	25	96.2 %
S2H14	22	22	100.0 %
S2M11	18	18	100.0 %
CV07-250	22	22	100.0 %
CV07-270	22	21	95.5~%
SB23	12	12	100.0 %
P2C-1F11	24	23	95.8 %
P2C-1A3	17	17	100.0 %
A fab	33	32	97.0~%
COVA1-16	24	22	91.7 %
S2E12	16	15	93.8~%
Fab 52	19	16	84.2 %
Fab 298	13	13	100.0 %
C1A	34	34	100.0 %
STE90-C11	35	32	91.4 %
P17	14	14	100.0 %
4A8	16	14	87.5 %
FC05	15	15	100.0 %
2G12	24	21	87.5 %

Table S1: The random coil percentages of antibody paratopes on the S protein.

The South Africa variant E484K and mutations F486L, F490S, S494P, and S494L will reduce P2C-1A3's competitiveness with ACE2.

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