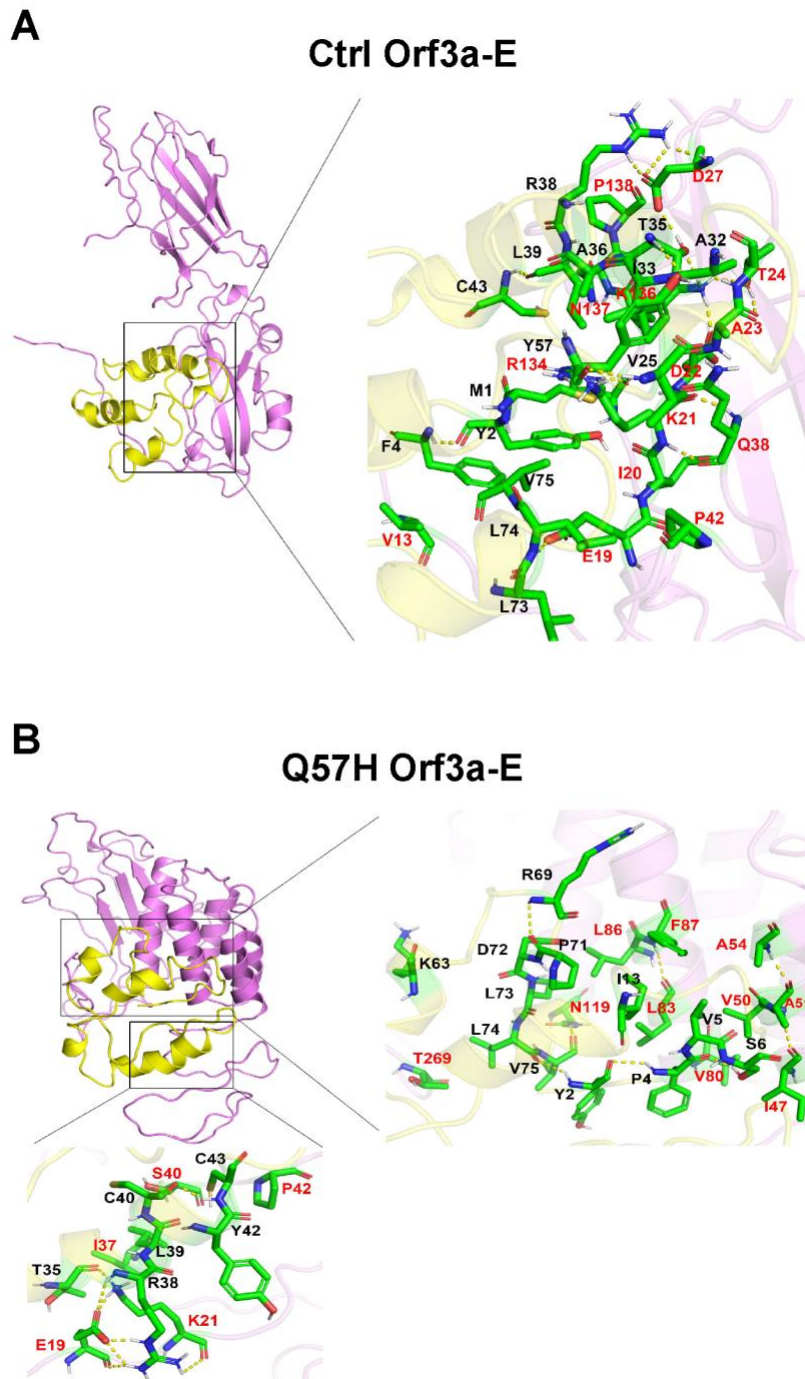**A**

Ctrl Orf3a-E

B

Q57H Orf3a-E

Figure S1. Hot spots within interactions between SARS-CoV-2 Orf3a and E
The hot spots in Ctrl Orf3a-E (A) or Q57H Orf3a-E (B) complexes are shown as
sticks. Control and mutant Orf3a are shown in violet, and E is shown in yellow. The
residues of Orf3a and docking proteins are colored in red and black, respectively.
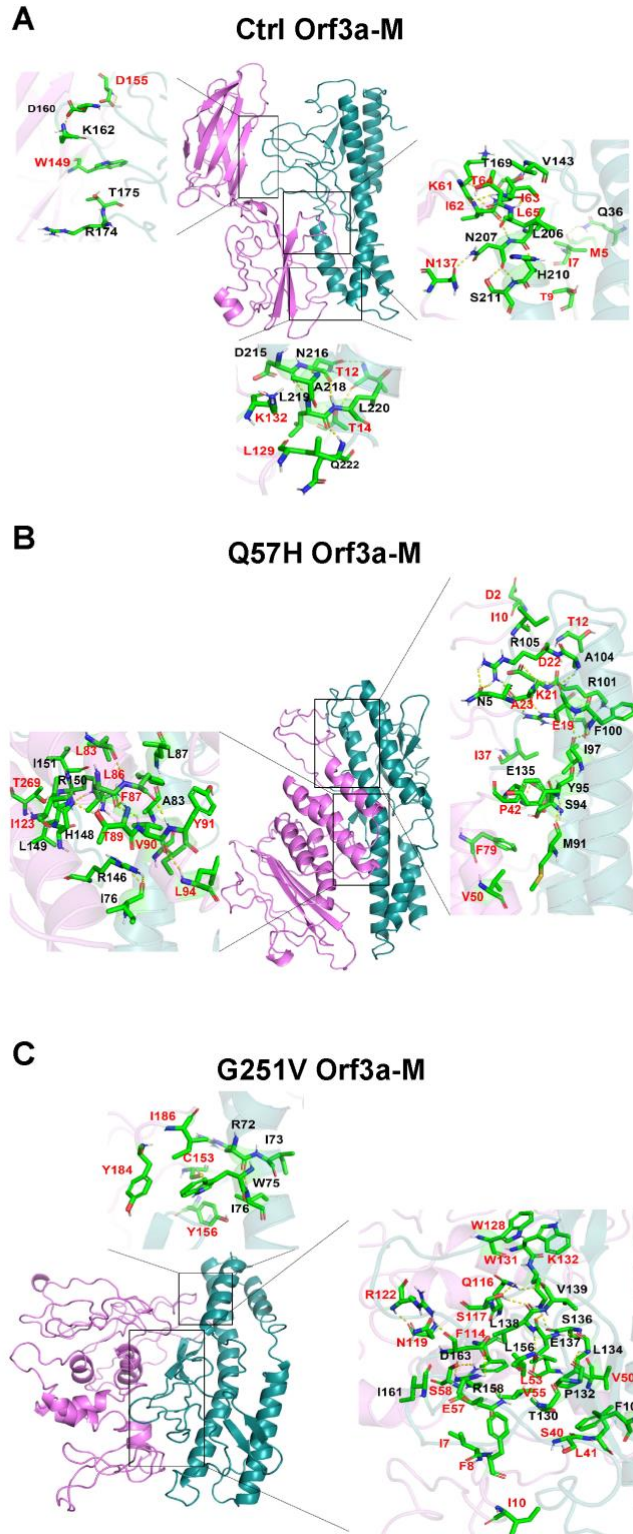
Figure S2. Hot spots within interactions between SARS-CoV-2 Orf3a and M
The hot spots in Ctrl Orf3a-M (A), Q57H Orf3a-M (B) or G251V Orf3a-M (C) complexes are shown as sticks. Control and mutant Orf3a are shown in violet, and M is shown in deep teal. The residues of Orf3a and docking proteins are colored in red and black, respectively.
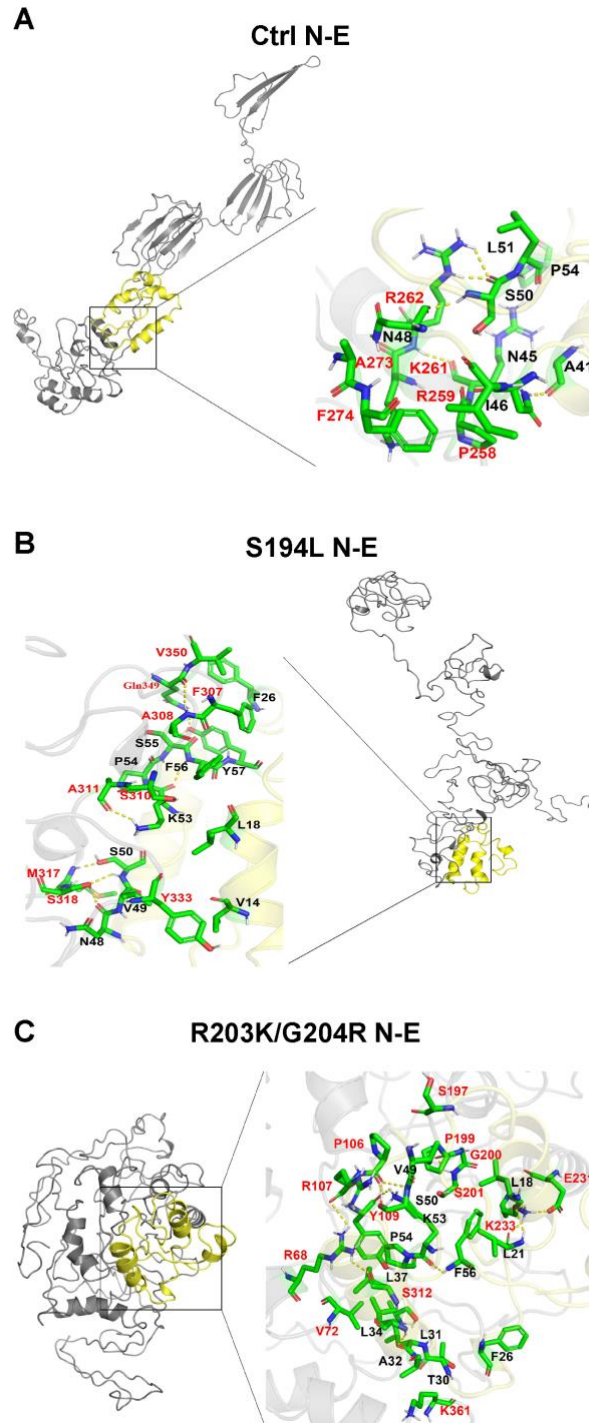
Figure S3. Hot spots within interactions between SARS-CoV-2 N and E
The hot spots in Ctrl N-E (A), S194L N-E (B) or R203K/G204R N-E (C) complexes
are shown as sticks. Control and mutant N are shown in grey, and E is shown in
yellow. The residues of N and docking proteins are colored in red and black,
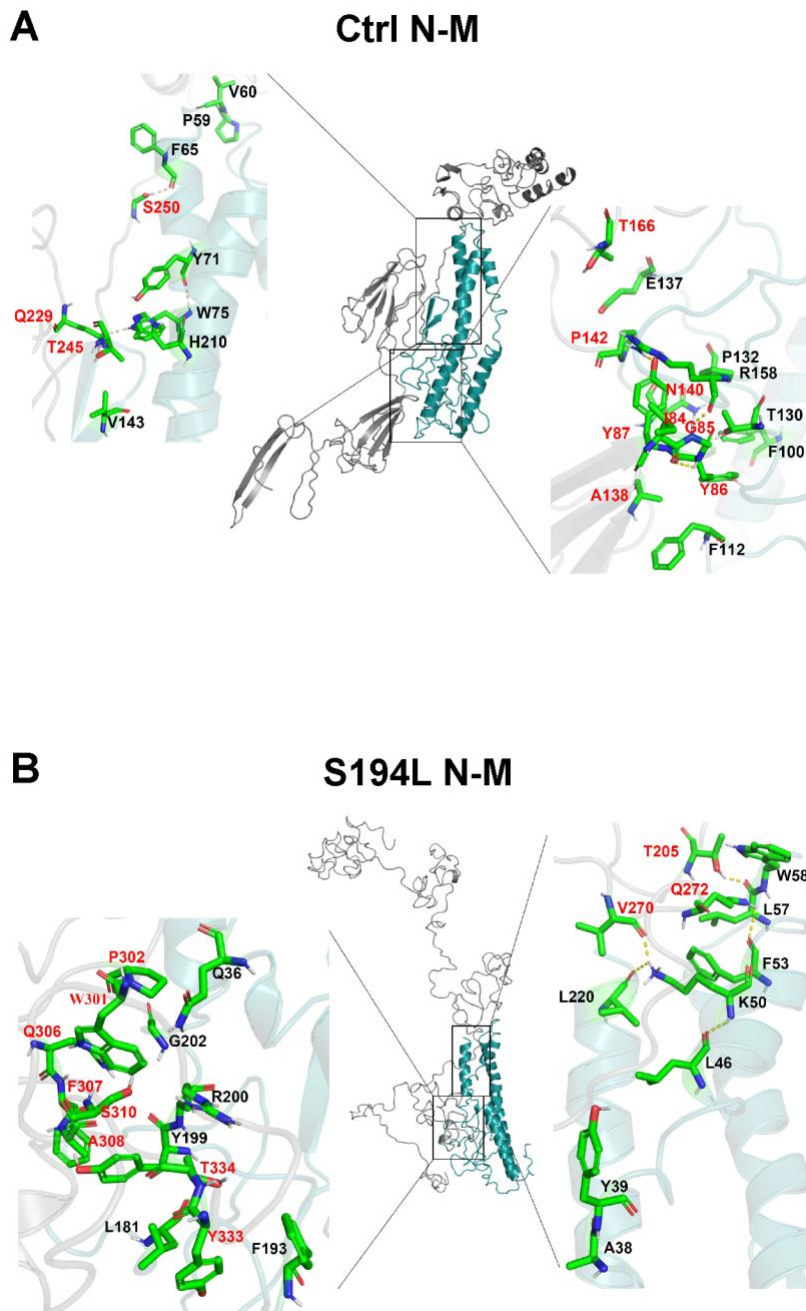respectively.

Figure S4. Hot spots within interactions between SARS-CoV-2 N and M
The hot spots in Ctrl N-M(A) or S194L N-M (B) complexes are shown as sticks.
Control and mutant N are shown in grey, and M is shown in deep teal. The residues
of N and docking proteins are colored in red and black, respectively.

Table S1. Information of SARS-CoV-2 mutations and protein models

Gene name/ Region	Base substitution(s)	Amino acid substitution(s)	Incidence	C-score	Estimated TM-score	TM-score (TM-align)	RMSD (TM-align)
nsp2	N/A	-	-	-1.48	0.53	-	-
	C1059T	T85I	0.1119	-1.57	0.52	0.9330	1.17
	A1163T	I120F	0.0375	-2.35	0.44	0.8740	0.84
nsp5	N/A	-	-	1.84	0.97	-	-
	G10097A	G15S	0.0133	1.86	0.98	0.9984	0.27
nsp6	N/A	-	-	-2.14	0.46	-	-
	G11083T	L36F	0.0441	-2.07	0.47	0.8721	2.55
nsp7	N/A	-	-	0.84	0.83	-	-
	C11916T	S25L	0.0122	0.93	0.84	0.9744	0.7
nsp12	N/A	-	-	-1.30	0.55	-	-
	C13730T	A97V	0.0100	-0.87	0.6	0.8703	1.08
	C14408T	P323L	0.4321	2.00	0.99	0.9996	0.14
nsp13	N/A	-	-	2.00	0.99	-	-
	C17747T/ A17858G	P503L/Y541C	0.0192	2.00	0.99	0.9992	0.24
S	G22992A	S447N	0.0334	-0.72	0.62	0.88387	2.32
	A23403G	D614G	0.4327	-1.40	0.54	0.8879	2.33
ORF3a	N/A	-	-	-3.14	0.36	-	-
	G25563T	Q57H	0.1512	-3.47	0.33	0.2244	6.42
	G26144T	G251V	0.0225	-4.38	0.26	0.2350	6.26
ORF8	N/A	-	-	-3.88	0.3	-	-
	T28144C	L84S	0.0380	-3.99	0.29	0.7689	2.67
	C27964T	S24L	0.0161	-3.59	0.32	0.7080	3.12
N	N/A	-	-	-1.58	0.52	-	-
	C28854T	S194L	0.0217	-0.34	0.67	0.2452	6.93
	C28311T	P13L	0.0105	-1.62	0.52	0.9585	2.08
	GGG28881-28883AAC	R203K/G204R	0.1784	-1.59	0.52	0.1841	7.59

Note: The data about SARS-CoV-2 mutations was collected from CNCB 2019nCoVR on

September 1st, 2020.