Cell, Volume *185*

Supplemental information

Structural basis of human ACE2 higher binding affinity to currently circulating Omicron SARS-CoV-2 sub-variants BA.2 and BA.1.1

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Table S1. Data collection and refinement statistics, Related to Figure 2

	Omicron BA.1.1	Omicron BA.2	Omicron BA.3
Data collection			
Space group	P41	P41212	P41212
Cell dimensions			
a, *b*, *c* (Å)	129.52, 129.52, 189.20	102.26, 103.26, 224.85	101.05, 101.05, 222.21
α, β, γ (°)	90, 90, 90	90.00, 90, 90.00	90, 90, 90
Wavelength (Å)	0.979	0.979	0.979
Resolution (Å)	50-3.00(3.11-3.00)	50-2.90 (3.00-2.90)	50-2.70 (2.80-2.70)
R_{merge}	0.173 (1.461)	0.190 (1.256)	0.148 (1.619)
R_{pim}	0.075 (0.635)	0 .064(0.452)	0.045 (0.408)
CC1/2	0.995 (0.639)	0.988 (0.727)	0.998 (0.642)
I / σI	11.3 (1.4)	13.3 (1.3)	16.6 (1.6)
Completeness (%)	99.9 (99.9)	96.5(97.8)	99.8(99.6)
No. reflections	62359	26827	32546
Redundancy	6.2 (6.1)	8.8 (8.3)	10.9(9.5)
Refinement			
Resolution (Å)	37.59-3.00	19.66-2.90	49.27-2.70
No. reflections	54430	26098	30027
R_{work} / R_{free}	0.1970 /0.2294	0.2156/0.2552	0.21.40/0.24.80
No. atoms			
Protein	13046	6556	6601
Ligand/ion	2	1	1
Water	0	0	0
B-factors			
Protein	57.9	58.0	50.5
Ligand/ion	53.8	66.1	69.6
Water			35.1
R.m.s. deviations			
Bond lengths (Å)	0.004	0.003	0.002
Bond angles (°)	0.668	0.535	0.519
Ramachandran plot			
Favored (%)	96.76	96.95	97.71
Allowed (%)	2.99	3.05	2.29
Outliers (%)	0.25	0	0

*Values in parentheses are for highest-resolution shell.

Table S2 Amino acid residues comparison of PT-RBD, Omicron BA.1-RBD, Omicron BA.1.1-RBD, Omicron BA.2-RBD, Omicron BA.3-RBD interacting with hACE2, Related to Figure 2

hACE2	PT-RBD	Omicron BA.1-RBD	Omicron BA.1.1-RBD	Omicron BA.2-RBD	Omicron BA.3-RBD
S19 (7/17/18/18/14)	A475 (3, **1**), G476 (4)	A475 (3, **1**), G476 (3), N477 (11, **1**)	A475 (2), G476 (3), N477 (13, **3**)	N477 (12, **4**), G476 (3), A475 (3, **1**)	N477 (11, **2**), A475 (3, **1**)
Q24 (24/22/21/31/26)	A475 (4), G476 (5), N487 (15, **1**)	A475 (3), G476 (5), N477 (1), N487 (13, **1**)	A475 (3), G476 (3), N477 (1), N487 (13, **1**), Y489 (1)	N487 (11, **2**), G476 (8), A475 (7), N477 (4), Y489 (1)	N487 (14, **2**), A475 (4), G476 (4), N477 (3, **1**), Y489 (1)
T27 (15/13/14/19/16)	F456 (5), Y473 (1), A475 (2), Y489 (7)	F456 (5), Y473 (1), A475 (2), Y489 (5)	F456 (5), Y473 (1), A475 (2), Y489 (6)	F456 (8), Y489 (6), Y473 (3), A475 (2)	F456 (6), Y489 (6), A475 (2), Y473 (2)
F28 (7/9/5/11/10)	Y489 (7)	Y489 (9)	Y489 (5)	Y489 (11)	Y489 (10)
D30 (10/2/3/10/5)	K417 (4, **1**), L455 (2), F456 (4)	L455 (1), F456 (1)	L455 (1), F456 (2)	F456 (5), L455 (5)	F456 (3), L455 (2)
K31 (19/15/15/25/16)	L455 (2), F456 (5), E484 (1), Y489 (6), F490 (2), Q493 (3)	L455 (1), F456 (4), Y489 (6), R493 (4),	F456 (6), Y489 (7), R493 (2)	Y489 (11), F456 (8), R493 (4), L455 (2)	Y489 (6), F456 (5), R493 (3), L455 (2)
H34 (20/29/34/23/22)	Y453 (5, **1**), L455 (9), Q493 (6)	Y453 (10, **2**), R493 (11), S494 (8)	N417 (2), Y453 (9, **2**), L455 (7), R493 (16)	L455 (10), Y453 (10, 1), N417 (2), R493 (1)	L455 (12), Y453 (7), N417 (2), R493 (1)
E35 (8/6/13/6/10)	Q493 (8)	R493 (6, **1**)	R493 (13,**2**)	R493 (6, **2**)	R493 (10, **1**)
E37 (7/2/2/1/1)	Y505 (7)	H505 (2)	H505 (2)	H505 (1)	H505 (1)
D38 (15/19/12/17/18)	Y449 (9, **1**), G496 (5), Q498 (1)	Y449 (7, **2**), S496 (6), R498 (5, **2**), Y501 (1)	R493 (6, **2**), S494 (1), S496 (5, **1**)	Y449 (9, **2**), R498 (6, **2**), Y501 (1), G496 (1)	Y449 (9, 2), R498 (6, **2**), G496 (2), Y501 (1)
Y41 (23/25/29/30/31)	Q498 (8), T500 (7, **1**), N501 (8, **1**)	R498 (3), T500 (7, **2**), Y501 (15)	R498 (6), T500 (9, **1**), Y501 (14)	Y501 (15), T500 (9, 2), R498 (6)	Y501 (17), T500 (8, **2**), R498 (6)
Q42 (16/9/8/12/11)	G446 (4, **1**), Y449 (4, 1), Q498 (8, **3**)	Y449 (2, **1**), R498 (7)	Y449 (1), R498 (7)	R498 (7), Y449 (5, **1**)	R498 (9), Y449 (2, **1**)
L45 (4/1/1/1/1)	Q498 (3), T500 (1)	T500 (1)	R498 (1)	T500 (1)	T500 (1)
L79 (2/2/1/2/3)	F486 (2)	F486 (2)	F486 (1)	F486 (2)	F486 (3)
M82 (9/7/12/21/13)	F486 (9)	F486 (7)	F486 (12)	F486 (21)	F486 (13)
Y83 (20/22/14/28/25)	F486 (11), N487 (8, **1**), Y489 (1)	F486 (11), N487 (10, **1**), Y489 (1, **1**)	F486 (8), N487 (5, **1**), Y489 (1)	N487 (13, **1**), F486 (12), Y489 (3, **1**)	N487 (11, **1**), F486 (11), Y489 (3, **1**)
N330 (8/8/4/8/9)	T500 (8)	T500 (8)	T500 (4)	T500 (8)	T500 (9)
K353 (50/57/49/60/57)	G496 (7, **1**), N501 (11), G502 (4, **1**), Y505 (28)	Y495 (1), S496 (2), Y501 (21), G502 (6, **1**), H505 (27)	S496 (2), Y501 (18), G502 (4, **1**), H505 (25)	H505 (29, **1**), Y501 (24), G502 (6, **1**), Y495 (1)	H505 (31), Y501 (20), G502 (6, **1**)
G354 (11/11/9/11/11)	G502 (7), Y505 (4)	G502 (7), H505 (4)	G502 (7), H505 (2)	G502 (7), H505 (4)	G502 (7), H505 (4)
D355 (9/8/10/14/13)	T500 (8, **1**), G502 (1)	T500 (7), G502 (1)	T500 (9, **2**), G502 (1)	T500 (11), G502 (3)	T500 (10), G502 (3)
R357 (3/3/3/5/5)	T500 (3)	T500 (3)	T500 (3, **1**)	T500 (5)	T500 (5)
R393 (1/0/0/0/0)	Y505 (1)				
Total	288, **16**	287, **16**	290, **17**	353,**18**	317,**15**

The numbers in parentheses of PT-RBD, Omicron BA.1-RBD, Omicron BA.1.1-RBD, Omicron BA.2-RBD, Omicron BA.3-RBD residues represent the number of vdw contacts between the indicated residues with hACE2. The numbers with underline suggest numbers of H-bonds and salt bridges between the pairs of residues. Vdw contact was analyzed at a cutoff of 4.5 Å and H-bonds/salt bridges at a cutoff of 3.5 Å.

Table S3. Number of contacts residues and different types of atom contacts formed between hACE2 and the four Omicron sub-variants, Related to Figure 2

	Number of contact residues*	Number of vdw contacts	Number of hydrogen bonds	Number of salt bridges	Total Number of atom contacts
BA.1	21/20	268	13	3	287
BA.1.1	21/20	257	13	4	277
BA.2	21/20	331	16	2	353
BA.3	21/19	298	13	2	317

* Number of hACE2 contact residues/number of RBD contact residues

Table S4. Comparison of MM/PBSA binding energy calculation results between BA.1 RBD/hACE2 complex and G496 BA.1 RBD/hACE2 systems, Related to Figure 3

	$\Delta E_{Binding}$		$\Delta\Delta E_{Binding}$ ($\Delta E_{Binding}$_G496 BA.1-$\Delta E_{Binding}$_BA.1) (kcal/mol)
	BA.1 RBD/hACE2 (kcal/mol)	G496 BA.1 RBD/hACE2 (kcal/mol)	
RBD-ACE2 [a]	-585.26 ± 1.12	-590.60 ± 1.12	-5.34
R408$_{RBD}$ [b]	-48.98 ± 0.12	-49.94 ± 0.10	-0.96
D38$_{ACE2}$ [b]	-23.16 ± 0.13	-24.00 ± 0.14	-0.84
S496/G496$_{RBD}$ [b]	1.12± 0.03	0.41 ± 0.01	-0.71
R498$_{RBD}$ [b]	-57.15 ± 0.09	-57.79 ± 0.09	-0.64
K440$_{RBD}$ [b]	-53.76 ± 0.18	-54.36 ± 0.15	-0.60
R403$_{RBD}$ [b]	-57.26 ± 0.07	-57.84 ± 0.07	-0.58

[a] Averaged binding energy calculated by MM/PBSA.

[b] Energy decomposition of single residues with favorable binding energies (ΔE_{G496} -$\Delta E_{S496} \leq$ -0.5 kcal·mol^{-1}).