

# Supporting Information

## Visualization of Interfacial Electrostatic Complementarity Reveals Evolutionary Changes in SARS-CoV-2 RBD–ACE2 Interactions

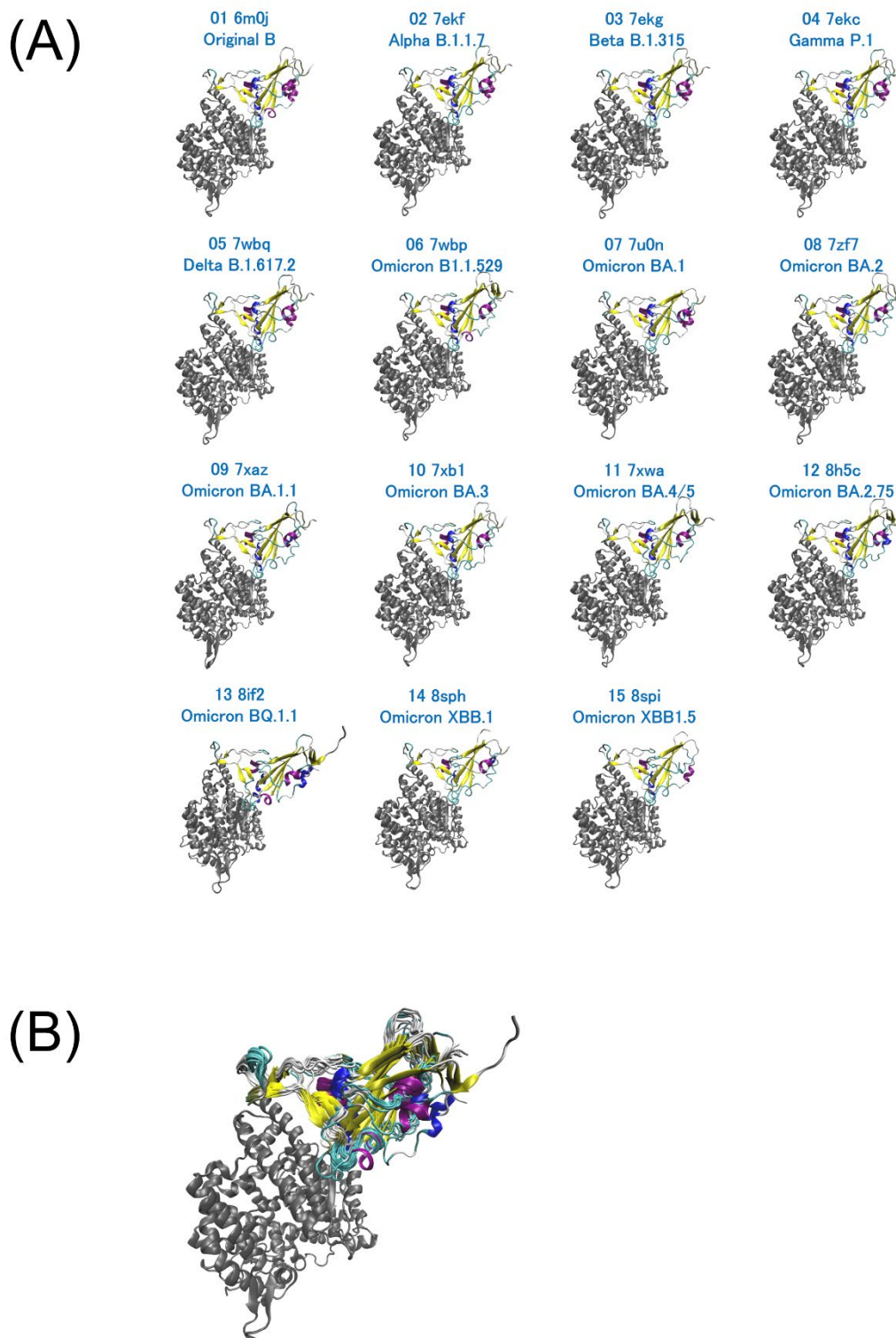
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**Figure S1:** Graphical representations of the complex structures of the 15 variants are shown in (A). A superimposed view of these 15 structures, aligned so that the hACE2 components overlap, is also provided in (B).



**Figure S2:** Alignment of the amino acid sequences of the RBDs from the 15 variants.

		330	340	350	360	370	380	390	400		
Original B		--	--TNLCPFGE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF		
Alpha	B. 1. 1. 7	--	--TNLCPFGE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF		
Beta	B. 1. 315	--	--TNLCPFGE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF		
Gamma	P. 1	--	--TNLCPFGE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF		
Delta	B. 1. 617. 2	--	--TNLCPFGE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	B1. 1. 529	--	--TNLCPFDE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	LAPFFTFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BA. 1	--	--NLCPFGE	VFNATKFPVS	YAWERKKISN	CVADYSVLN	STFFSTFKCY	GVSATKLNDL	CFSNVYADSF		
Omicron	BA. 2	--	--NLCPFDE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	FAPFFAFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BA. 1. 1	--	--TNLCPFDE	VFNATKFPVS	YAWNRRKRISN	CVADYSVLN	LAPFFTFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BA. 3	--	--TNLCPFDE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	FAPFFTFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BA. 4/5	--	--TNLCPFDE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	FAPFFAFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BA. 2. 75	--	--TNLCPFHE	VFNATRFASV	YAWNRRKRISN	CVADYSVLN	FAPFFAFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	BQ. 1. 1	FP	NITNLCPFDE	VFNATTFASV	YAWNRRKRISN	CVADYSVLN	FAPFFAFKCY	GVSPTKLNDL	CFTNVYADSF		
Omicron	XBB. 1	--	--NLCPFGE	VFNATKFPVS	YAWERKKISN	CVADYSVLN	STFFSTFKCY	GVSATKLNDL	CFSNVYADSF		
Omicron	XBB1. 5	--	-----	VFNATKFPVS	YAWERKKISN	CVADYSVLN	STFFSTFKCY	GVSATKLNDL	CFSNVYADSF		
***** *.*. ***'.**.*.*** ***** : * :**** ***, ***** **':*****											
		410	420	430	440	450	460	470	480	490	500
Original B		VIRGDEVQRI	APGQTGKIAD	YNYKLDDFT	GCVIAWNSNN	LDSKVGGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGSTPC	NGVEGFNCYF	PLQSYGFQPT
Alpha	B. 1. 1. 7	VIRGDEVQRI	APGQTGKIAD	YNYKLDDFT	GCVIAWNSNN	LDSKVGGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGSTPC	NGVEGFNCYF	PLQSYGFQPT
Beta	B. 1. 315	VIRGDEVQRI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSNN	LDSKVGGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGSTPC	NGV <del>K</del> GFNCYF	PLQSYGFQPT
Gamma	P. 1	VIRGDEVQRI	APGQTGT <del>I</del> AD	YNYKLDDFT	GCVIAWNSNN	LDSKVGGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGSTPC	NGV <del>K</del> GFNCYF	PLQSYGFQPT
Delta	B. 1. 617. 2	VIRGDEVQRI	APGQTGKIAD	YNYKLDDFT	GCVIAWNSNN	LDSKVGGNYN	Y <del>R</del> YRLFRKSN	LKPFERDIST	EIYQAGS <del>K</del> PC	NGVEGFNCYF	PLQSYGFQPT
Omicron	B1. 1. 529	VIRGDEVQRI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKV <del>S</del> GGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGFNCYF	PL <del>R</del> SYS <del>F</del> RPT
Omicron	BA. 1	V <del>V</del> KGD <del>D</del> VRQI	APGQTGV <del>I</del> AD	YNYKLDDF <del>M</del>	GCVLAWNTRN	IDATSTGNYN	Y <del>K</del> YRLFRKSN	LKPFERDIST	EIYQAGSTPC	NGVAGFNCYF	PL <del>R</del> SYS <del>F</del> RPT
Omicron	BA. 2	VIRGNE <del>V</del> SQI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKVGGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGFNCYF	PL <del>R</del> SYS <del>F</del> RPT
Omicron	BA. 1. 1	VIRGDEVQRI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKV <del>S</del> GGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGFNCYF	PL <del>R</del> SYS <del>F</del> RPT
Omicron	BA. 3	VIRGNE <del>V</del> SQI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKV <del>S</del> GGNYN	YLRLFRKSN	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGFNCYF	PL <del>R</del> SYS <del>F</del> RPT
Omicron	BA. 4/5	VIRGNE <del>V</del> SQI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKVGGNYN	Y <del>R</del> YRLFRKSN	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGVNCYF	PLQSYGFRPT
Omicron	BA. 2. 75	VIRGNE <del>V</del> SQI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDSKV <del>S</del> GGNYN	YLRLFRKS <del>K</del>	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGFNCYF	PLQSYGFRPT
Omicron	BQ. 1. 1	VIRGNE <del>V</del> SQI	APGQTGN <del>I</del> AD	YNYKLDDFT	GCVIAWNSN <del>K</del>	LDS <del>T</del> VGGNYN	Y <del>R</del> YRLFRKS <del>K</del>	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGVNCYF	PLQSYGFRPT
Omicron	XBB. 1	V <del>V</del> KGD <del>D</del> VRQI	APGQTGV <del>I</del> AD	YNYKLDDF <del>M</del>	GCVLAWNTRN	IDATSTGNYN	Y <del>K</del> YRLFRKS <del>K</del>	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGSN <del>C</del> YS	PLQSYGFRPT
Omicron	XBB1. 5	V <del>V</del> KGD <del>D</del> VRQI	APGQTGV <del>I</del> AD	YNYKLDDF <del>M</del>	GCVLAWNTRN	IDATSTGNYN	Y <del>K</del> YRLFRKS <del>K</del>	LKPFERDIST	EIYQAGN <del>K</del> PC	NGVAGPNCYS	PLQSYGFRPT
*.:*::: ** ***** **' ***** **':*****::: :*.: ***** * *****: ***** *****:..** *** * *** **'.**.*.***											
		510	520								
Original B		NGVGYPYRV	VVLSFELLHA	PATVCG-							
Alpha	B. 1. 1. 7	YGVGYQPYRV	VVLSFELLHA	PATVCGP							
Beta	B. 1. 315	YGVGYQPYRV	VVLSFELLHA	PATVCGP							
Gamma	P. 1	YGVGYQPYRV	VVLSFELLHA	PATVCGP							
Delta	B. 1. 617. 2	NGVGYPYRV	VVLSFELLHA	PATVCGP							
Omicron	B1. 1. 529	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BA. 1	YGVGHQPYRV	VVLSFEL <del>T</del> V	-----							
Omicron	BA. 2	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BA. 1. 1	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BA. 3	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BA. 4/5	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BA. 2. 75	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	BQ. 1. 1	YGVGHQPYRV	VVLSFELLHA	PATVCGP							
Omicron	XBB. 1	YGVGHQPYRV	VVLSFELLNA	P-----							
Omicron	XBB1. 5	YGVGHQPYRV	VVLSFELLNA	P-----							
***:***** *****											

**Figure S3:** Visualization of the pESP at the CGCs for the complexes of the 15 variants. Results are provided for the cases without neutralization, with charge-removed neutralization, and constant-added neutralization. The  $R^-$  and  $D^-$  values are also provided.

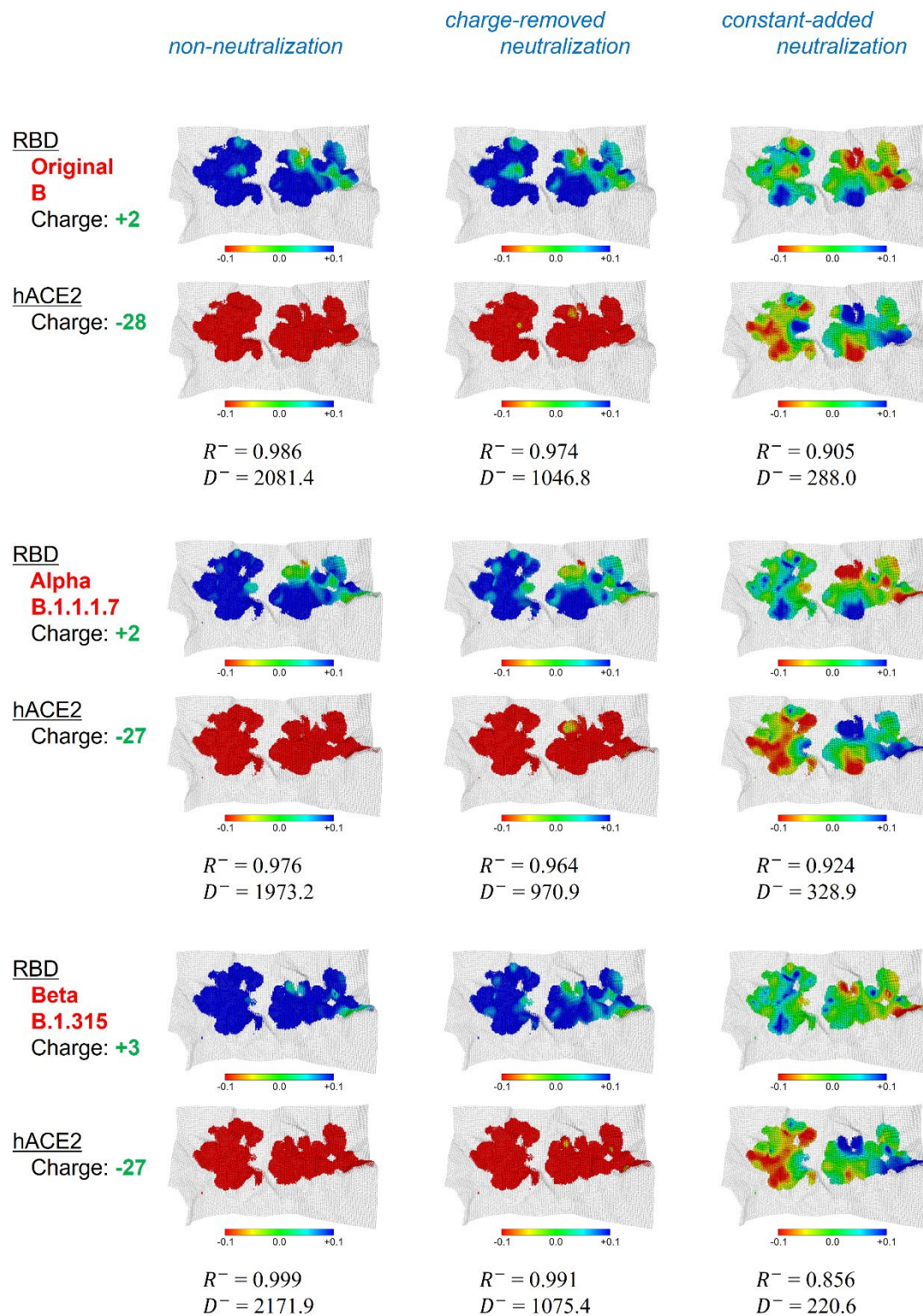




Figure S3 (continued)

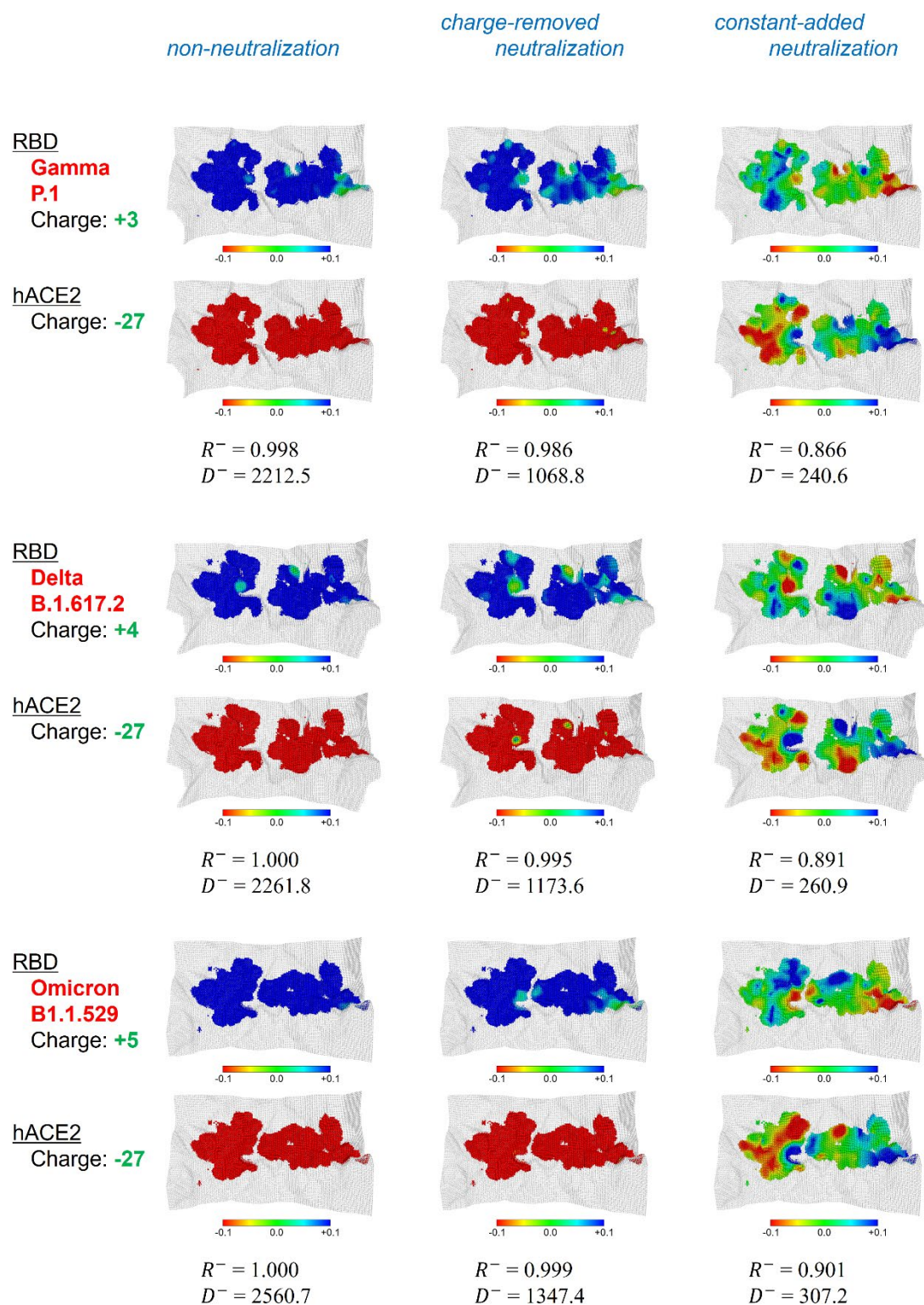


Figure S3 (continued)

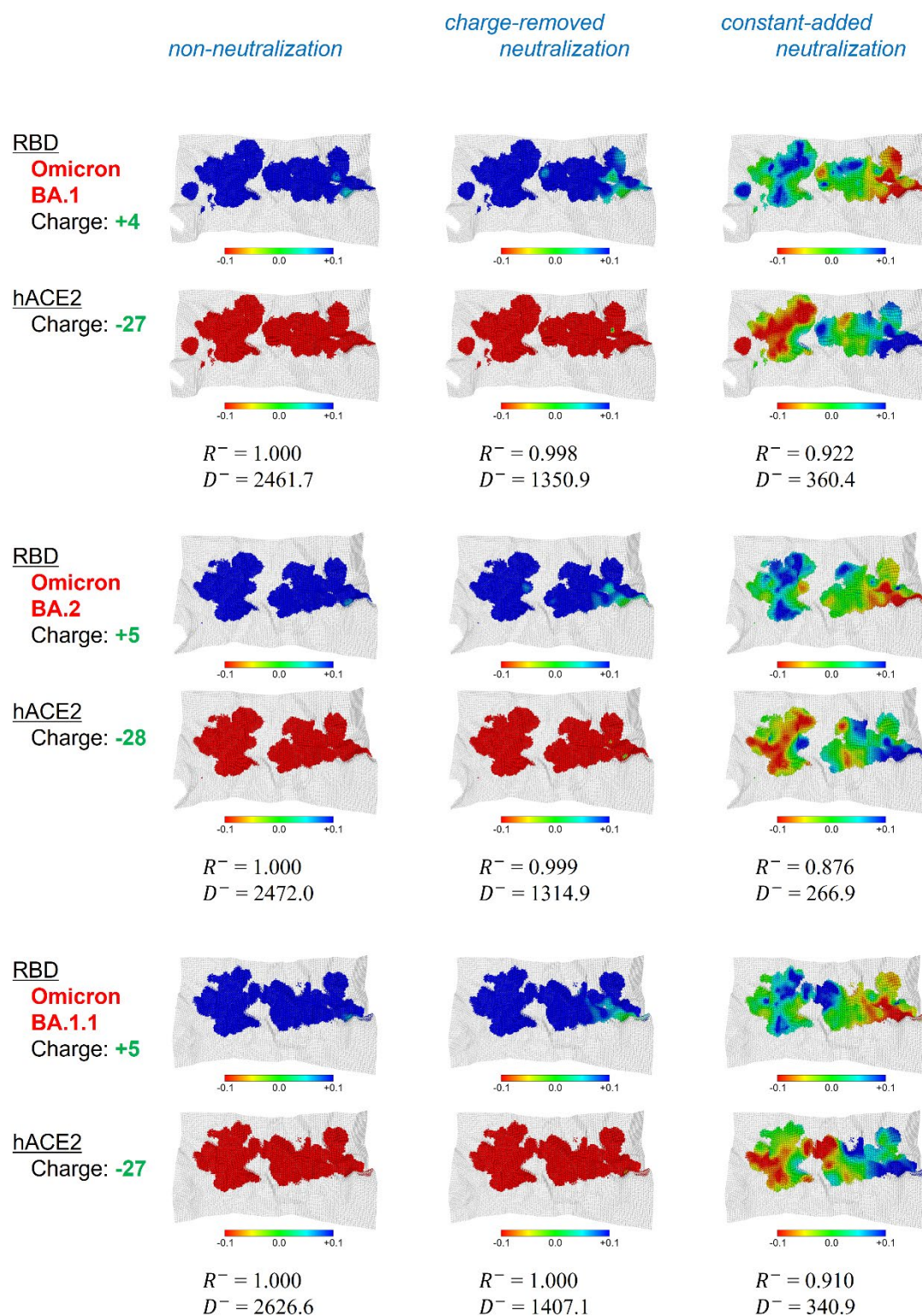




Figure S3 (continued):

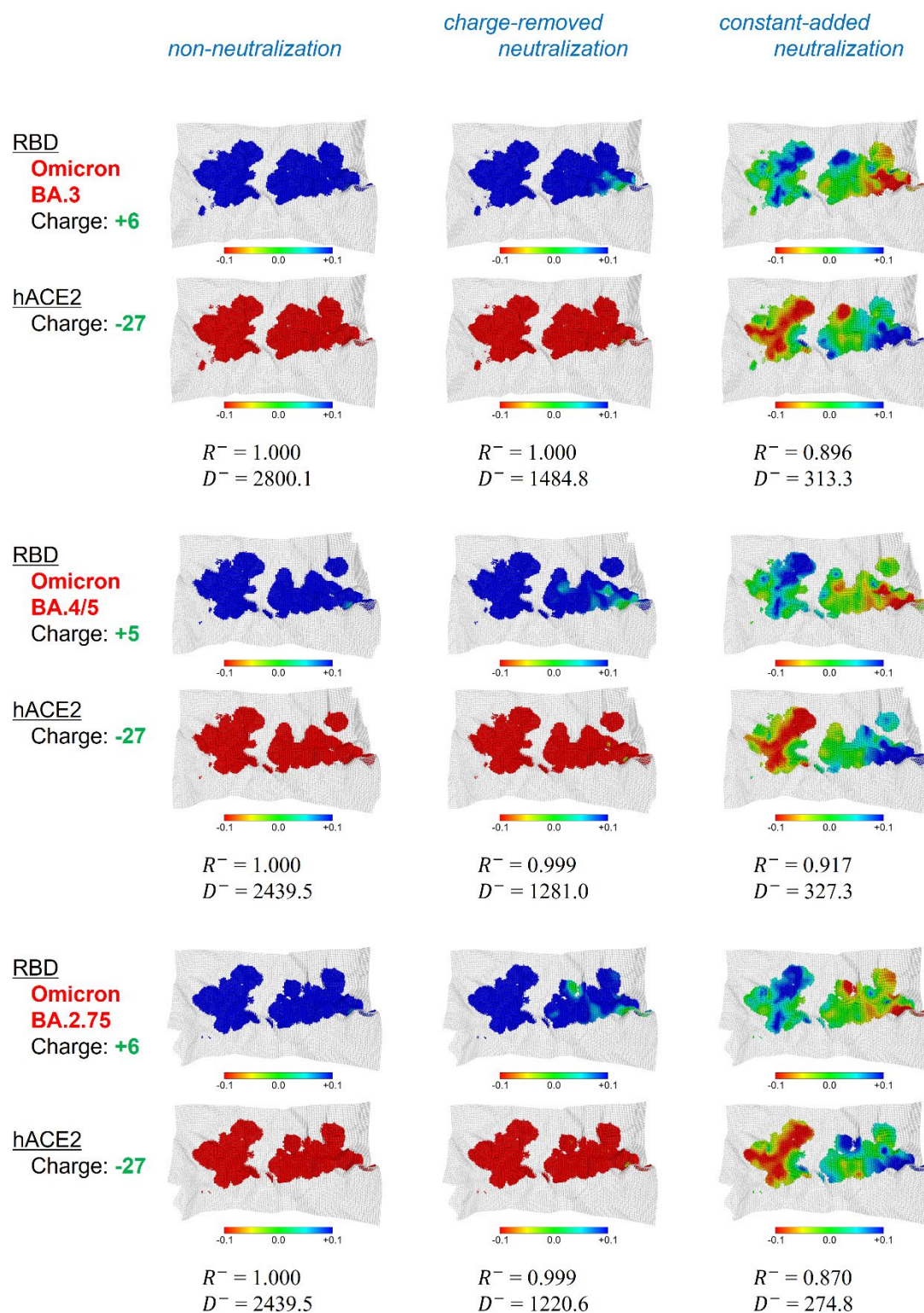
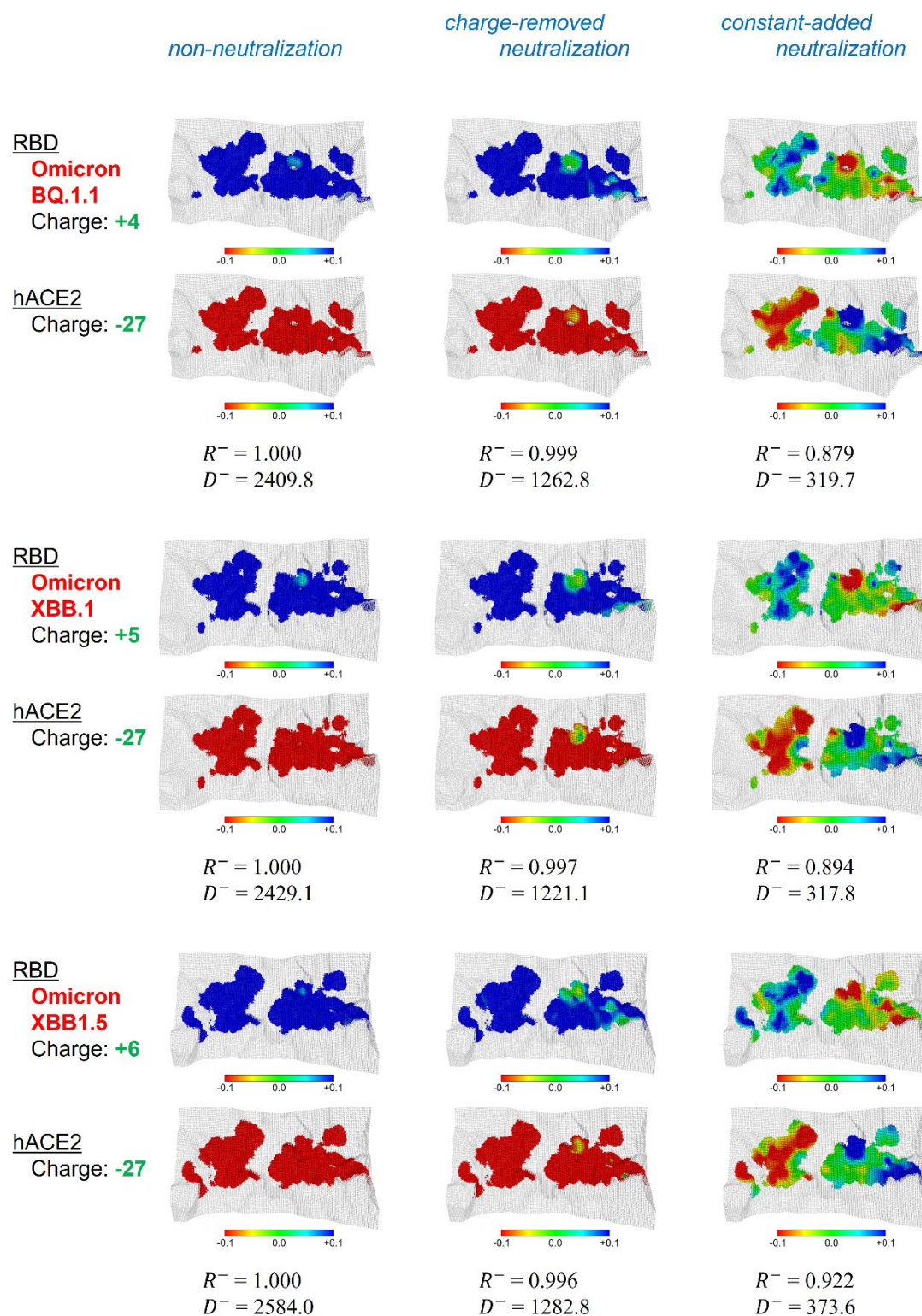


Figure S3 (continued):





**Figure S4:** Visualization of the isolated protein's ESP at the CGCs for the 15 variants. Results are provided for the cases without neutralization, with charge-removed neutralization, and constant-added neutralization. The  $R^-$  and  $D^-$  values are also provided. Values in parentheses indicate the differences from the corresponding values of the pESP of the complexes.

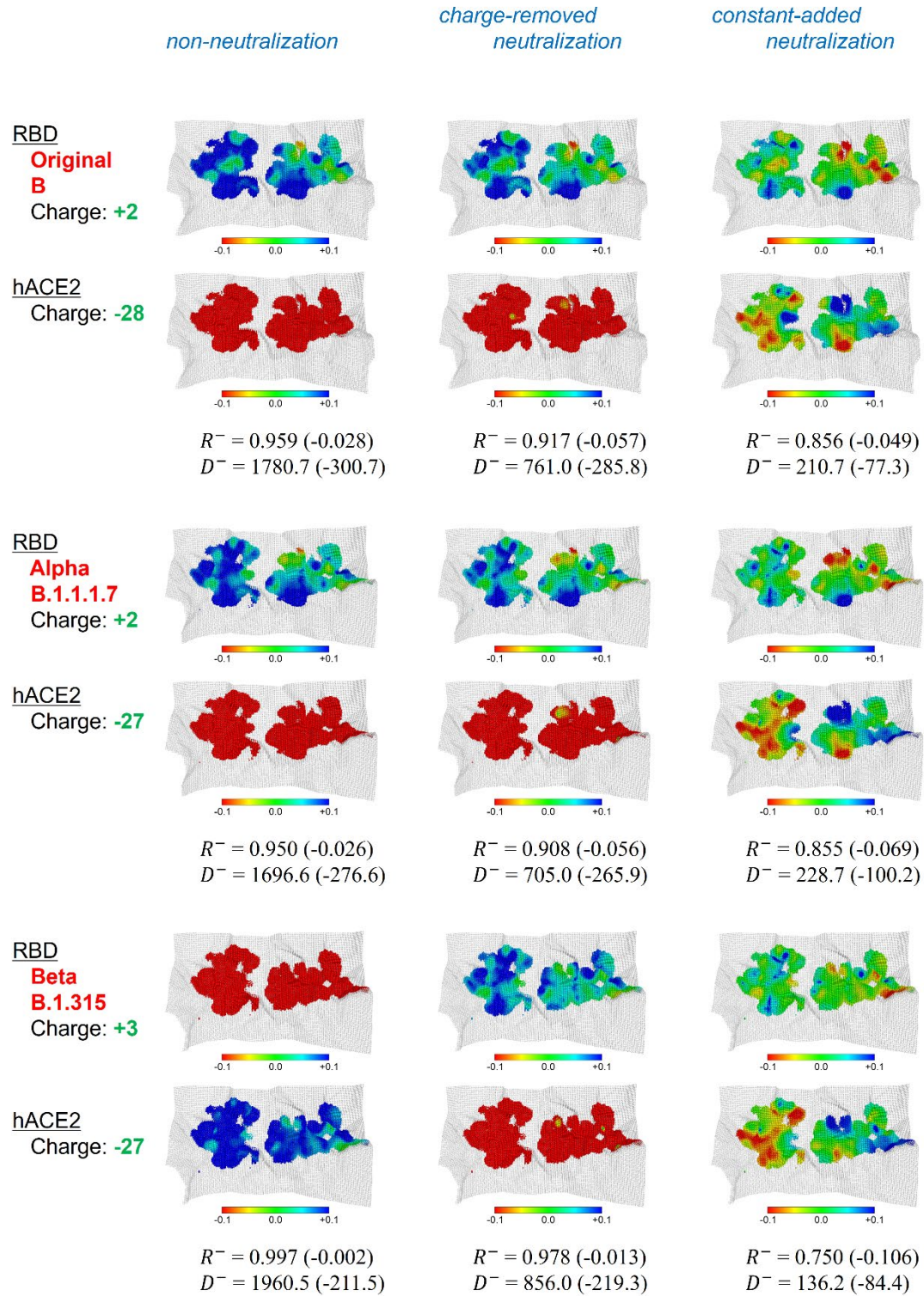


Figure S4(continued)

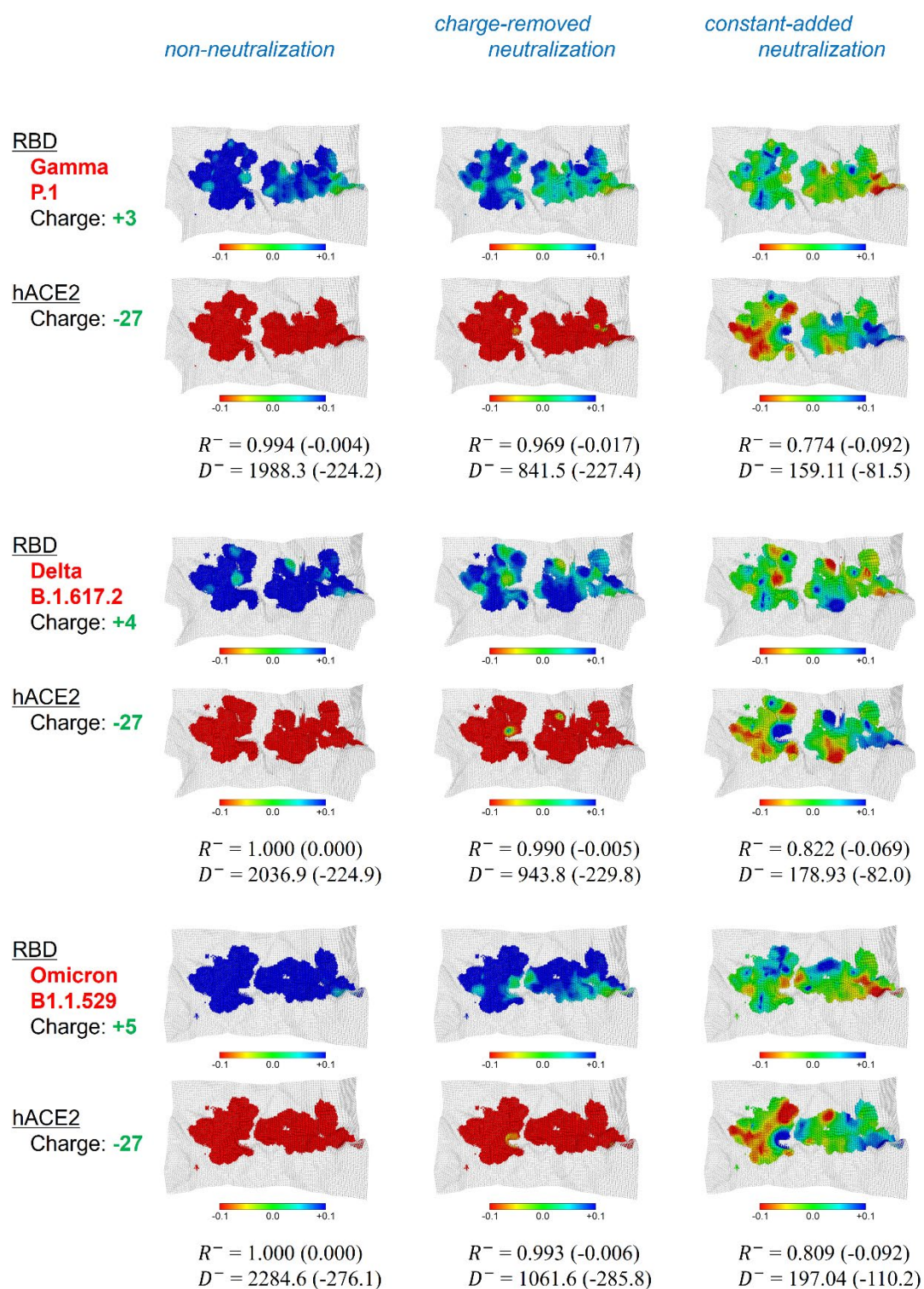




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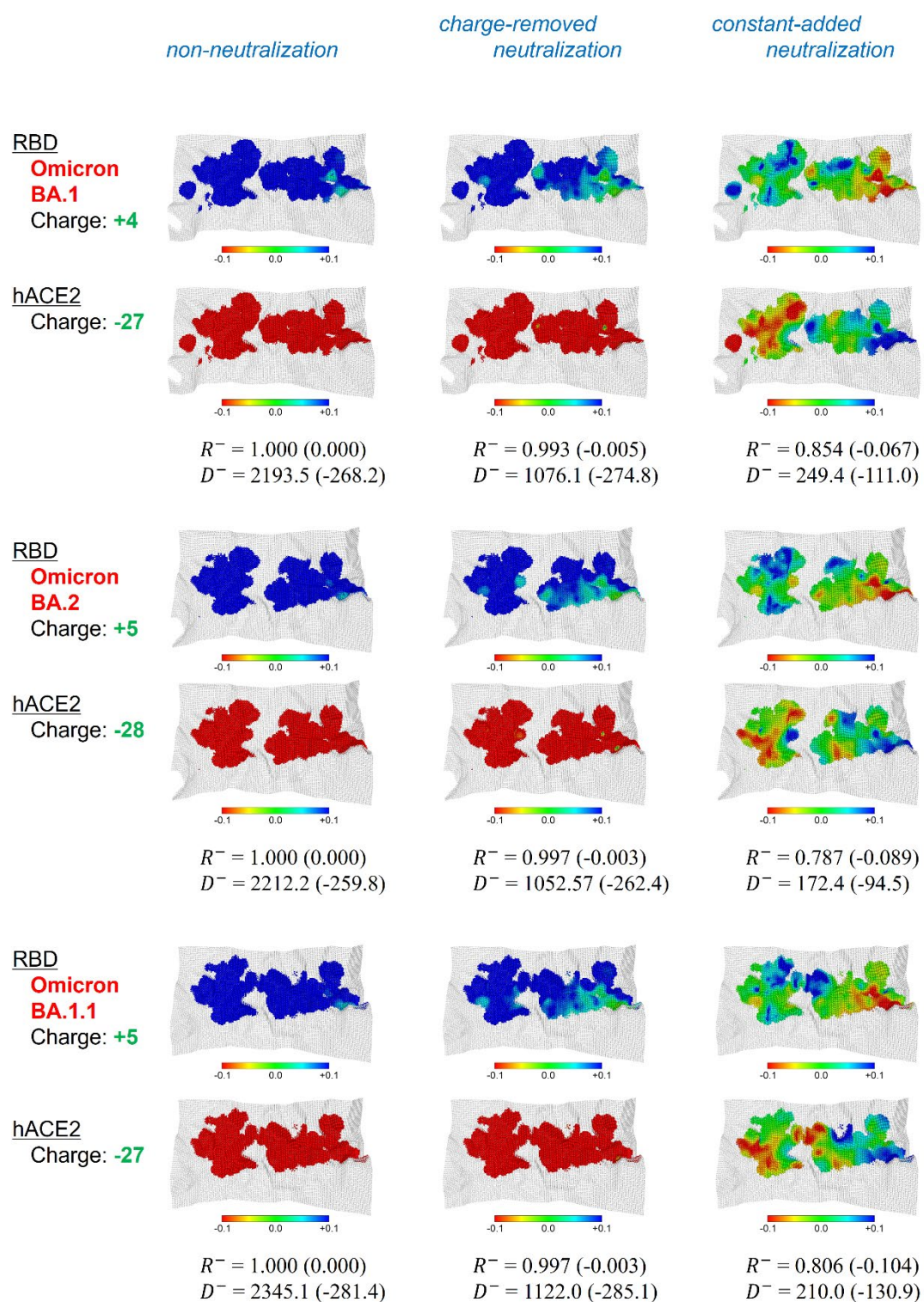




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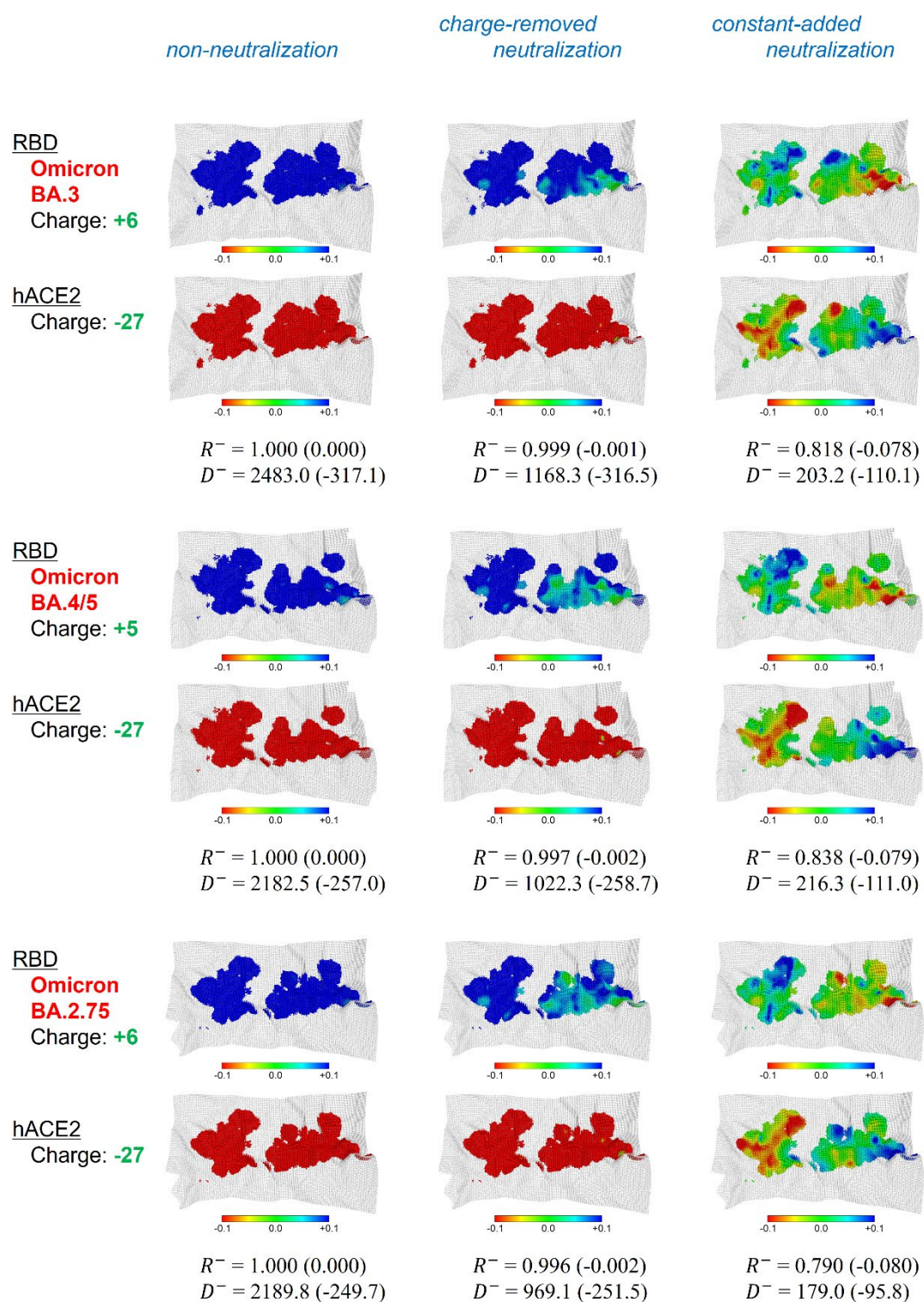
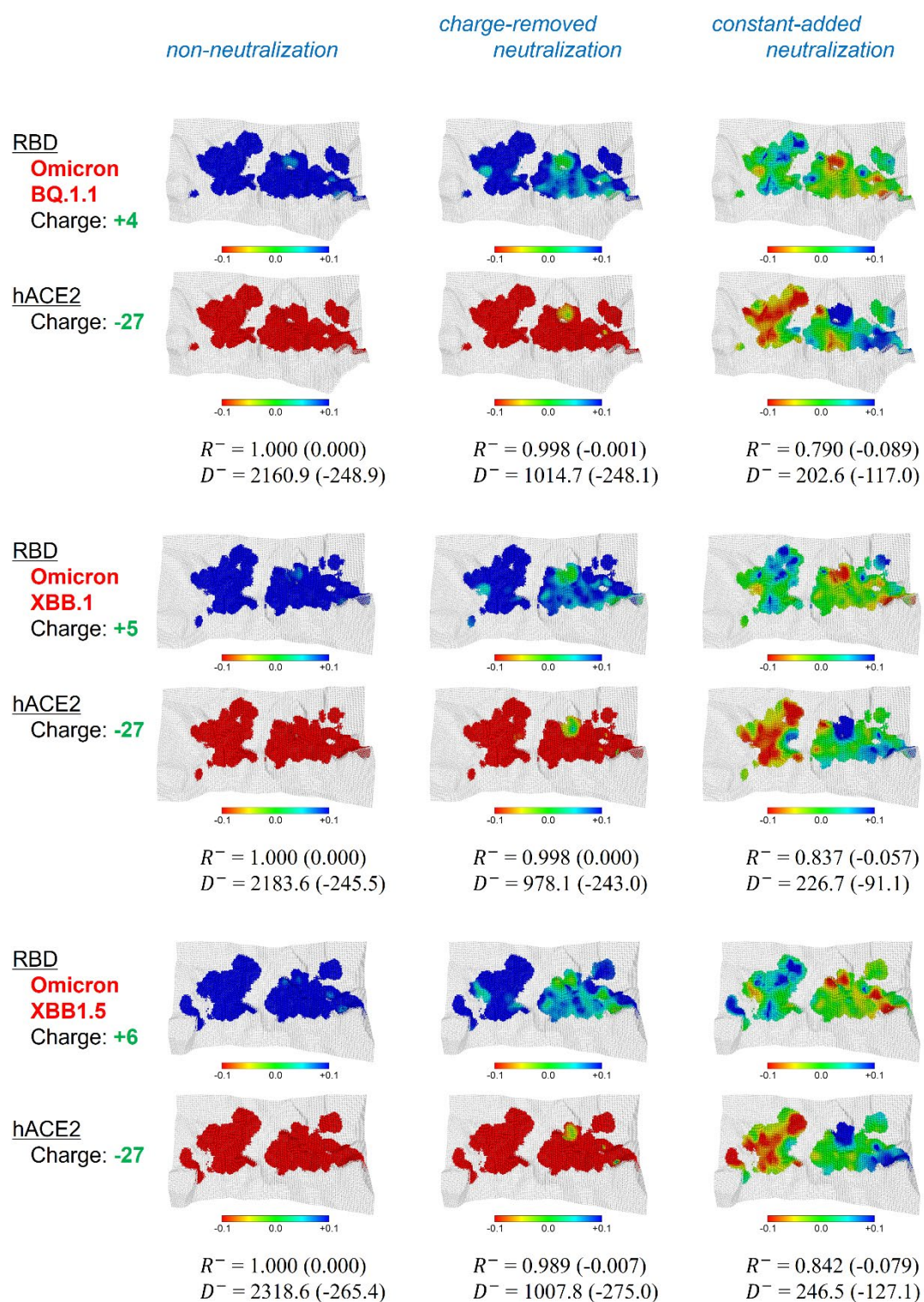


Figure S4(continued):





**Figure S5:** Visualization of the pEDN (i.e., the  $\rho_t^A + \rho_t^B$ ) at the CGCs for the complexes of the 15 variants, along with the EDN of the corresponding isolated proteins. The  $\rho^+$  values are also provided.

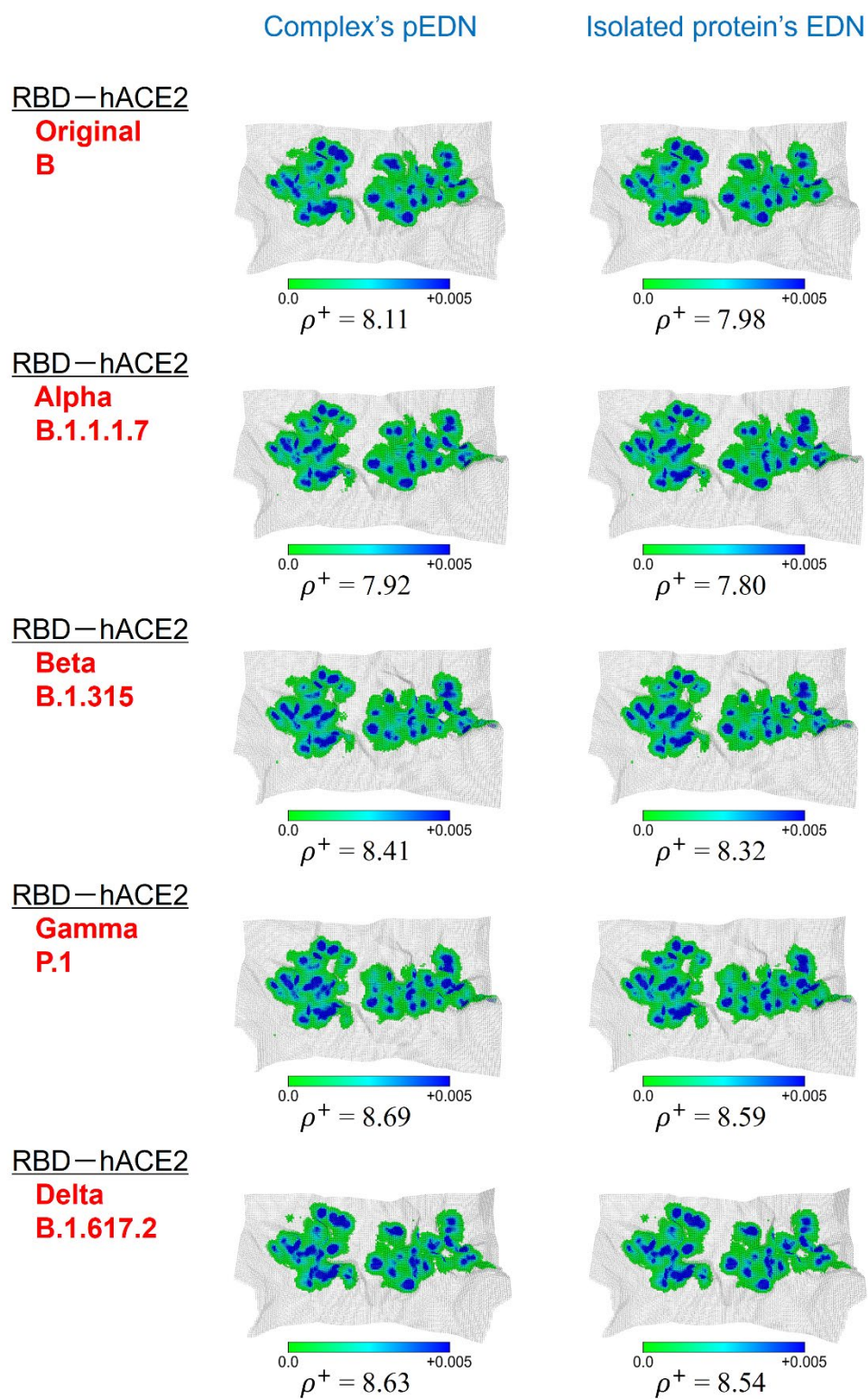




Figure S5(continued)

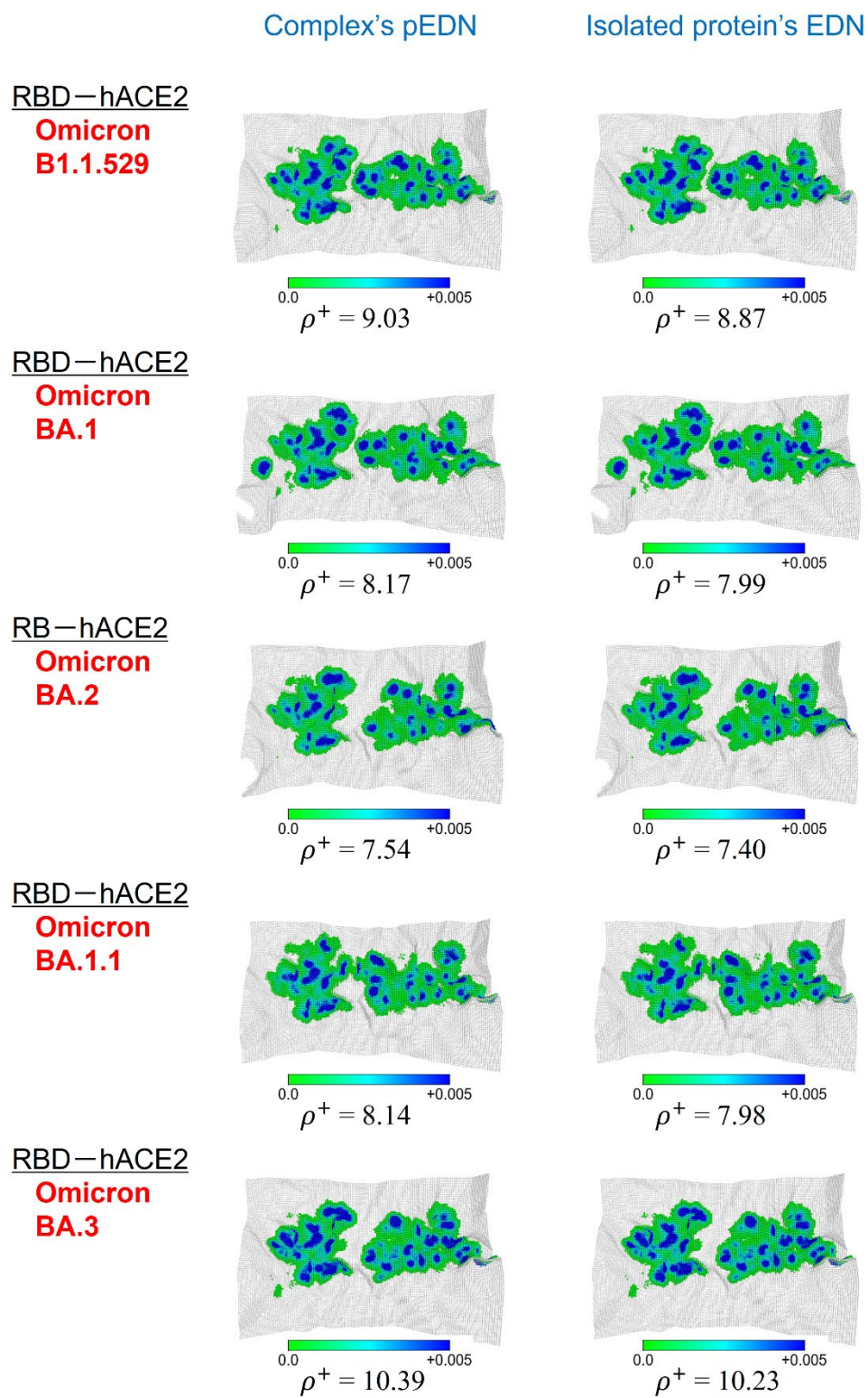
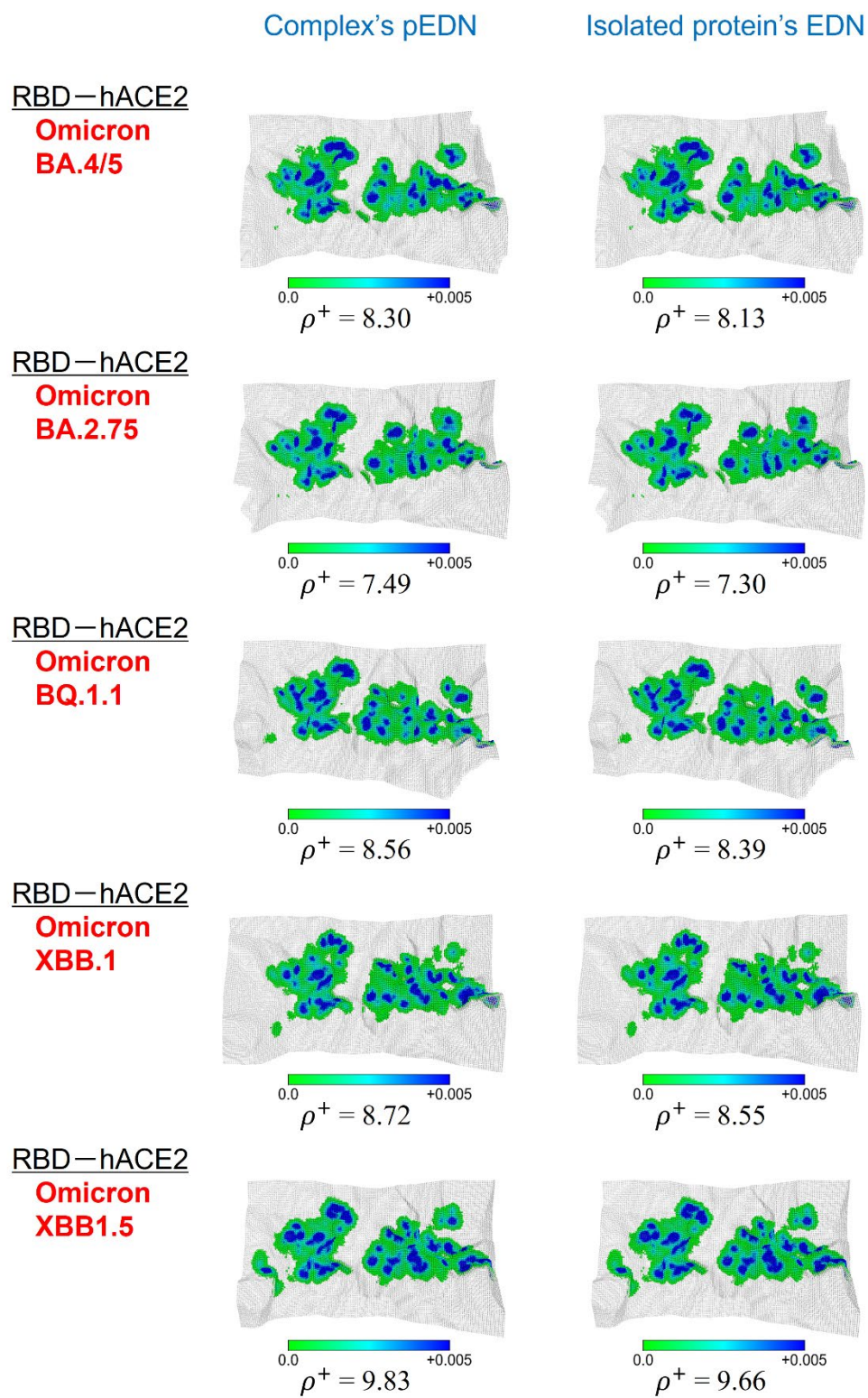
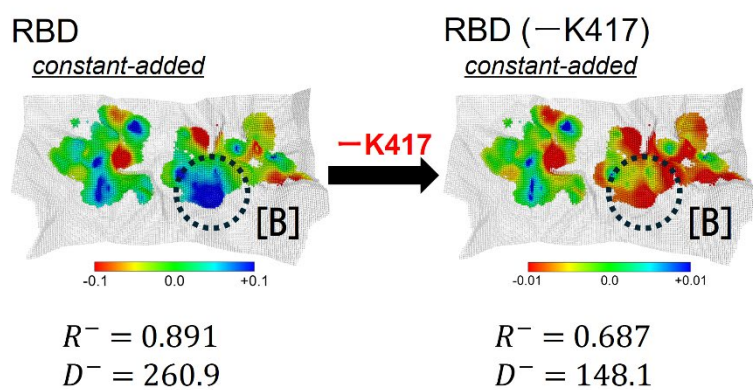


Figure S5(continued)

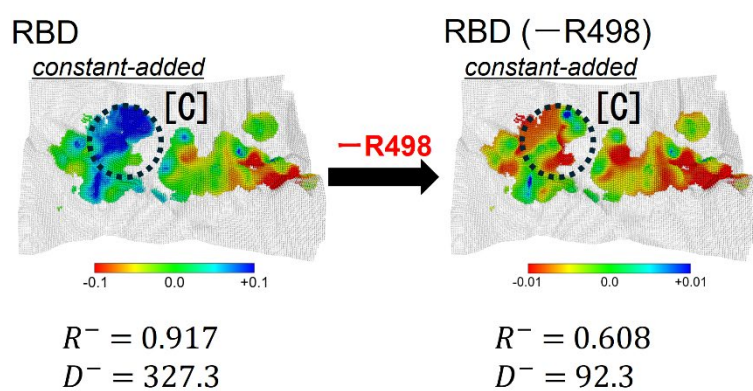


**Figure S6:** Visualization of the pESP of the RBDs after excluding the contributions of selected amino acids. Constant-added neutralization was applied. The  $R^-$  and  $D^-$  values are also provided.

(A) Delta (B.1.617.2)

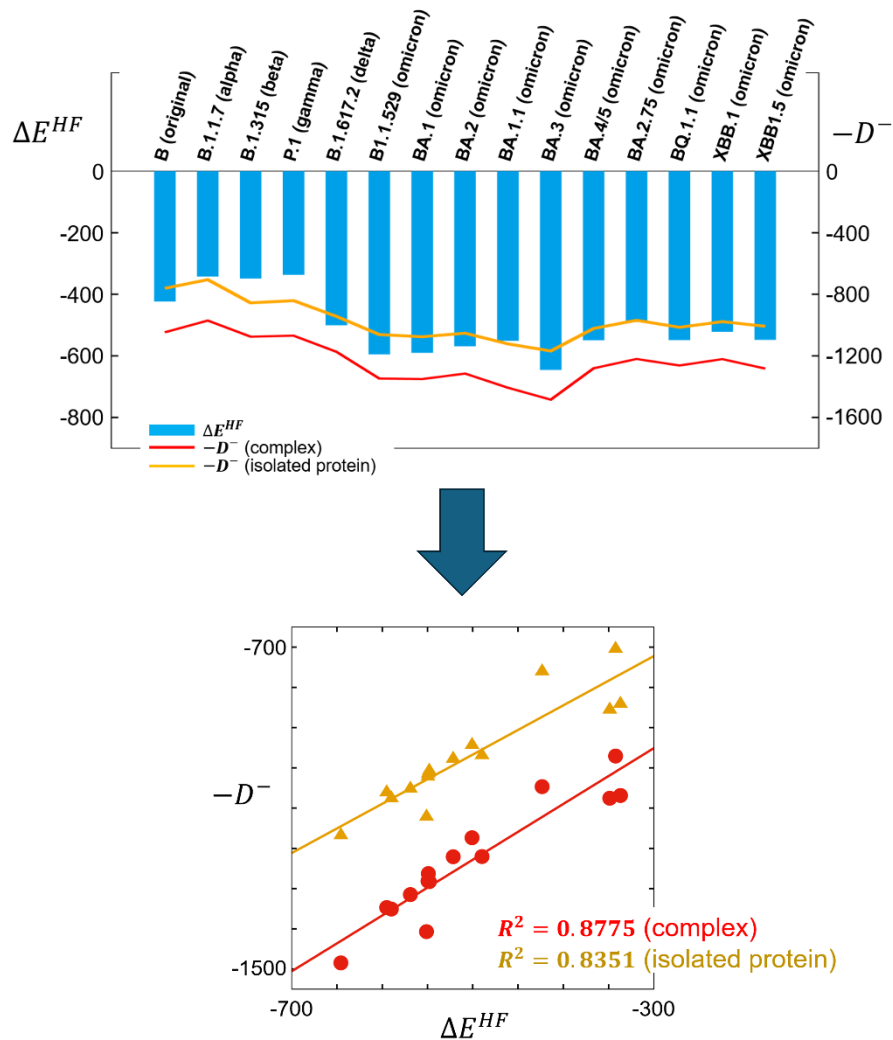


(B) Omicron (BA.4/5)

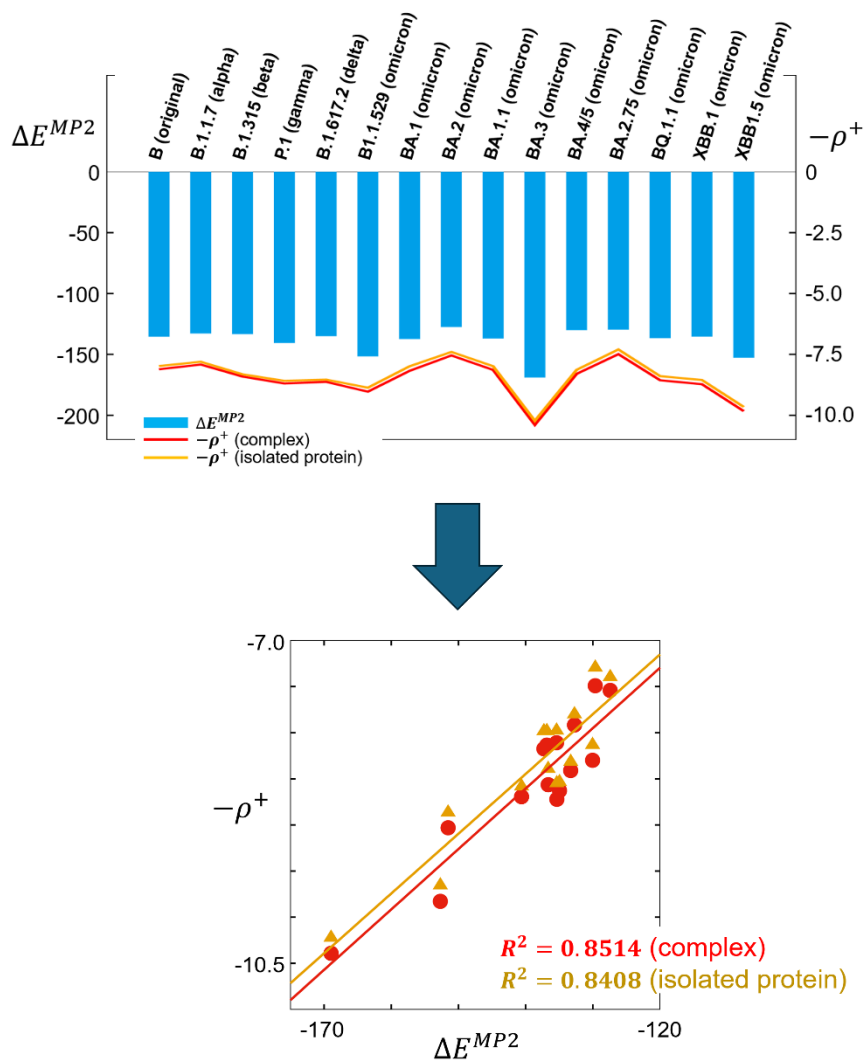




**Figure S7:** A scatter plot showing the correlation between the  $D^-$  values and the electrostatic interaction energies ( $\Delta E^{HF}$ ) obtained from the FMO calculations. Here, the  $D^-$  values with charge-removed neutralization. The detailed definition of  $\Delta E^{HF}$  is described in previous paper [H. Ozono, et al., J. Phys. Chem. B, 2022, 126 (42), 8415].



**Figure S8:** A scatter plot showing the correlation between the  $\rho^+$  values and the total MP2 correlation energies ( $\Delta E^{MP2}$ ) obtained from the FMO calculations. The detailed definition of  $\Delta E^{MP2}$  is described in previous paper [H. Ozono, et al., J. Phys. Chem. B, 2022, 126 (42), 8415].



**Figure S9:** MP2 correlation energies of individual amino acid residues near the interface for the 15 complexes. These values were obtained from the IFIE analysis in the FMO method. Energies of the amino acids for the RBDs are shown on the left-hand side, and those for hACE2 are shown on the right-hand side. Amino acids highlighted in green indicate mutations from the original strain. Cysteine residues forming a disulfide bond were treated as a single fragment in our calculations; therefore, their energies are provided as combined values.

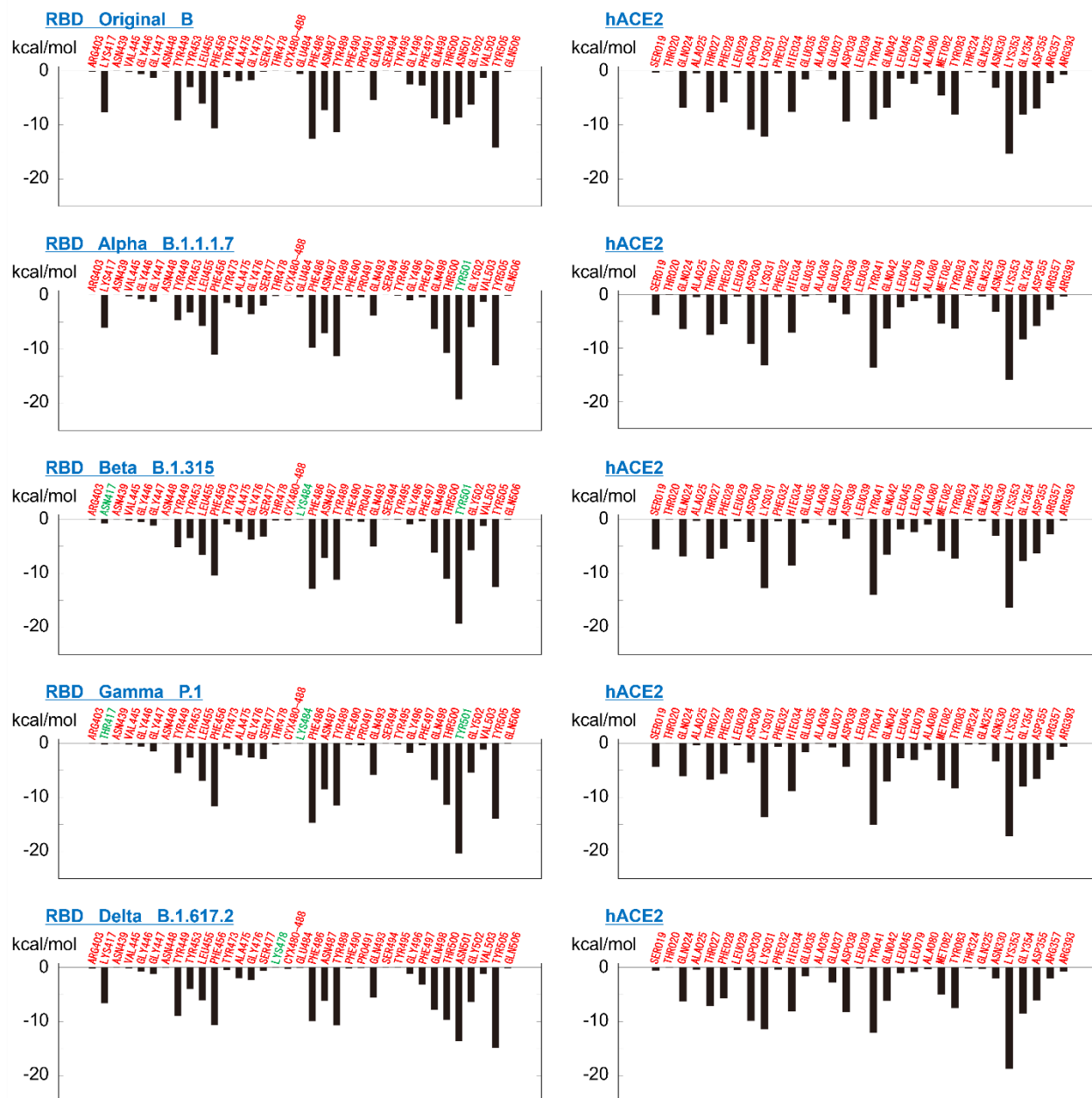




Figure S9(continue)

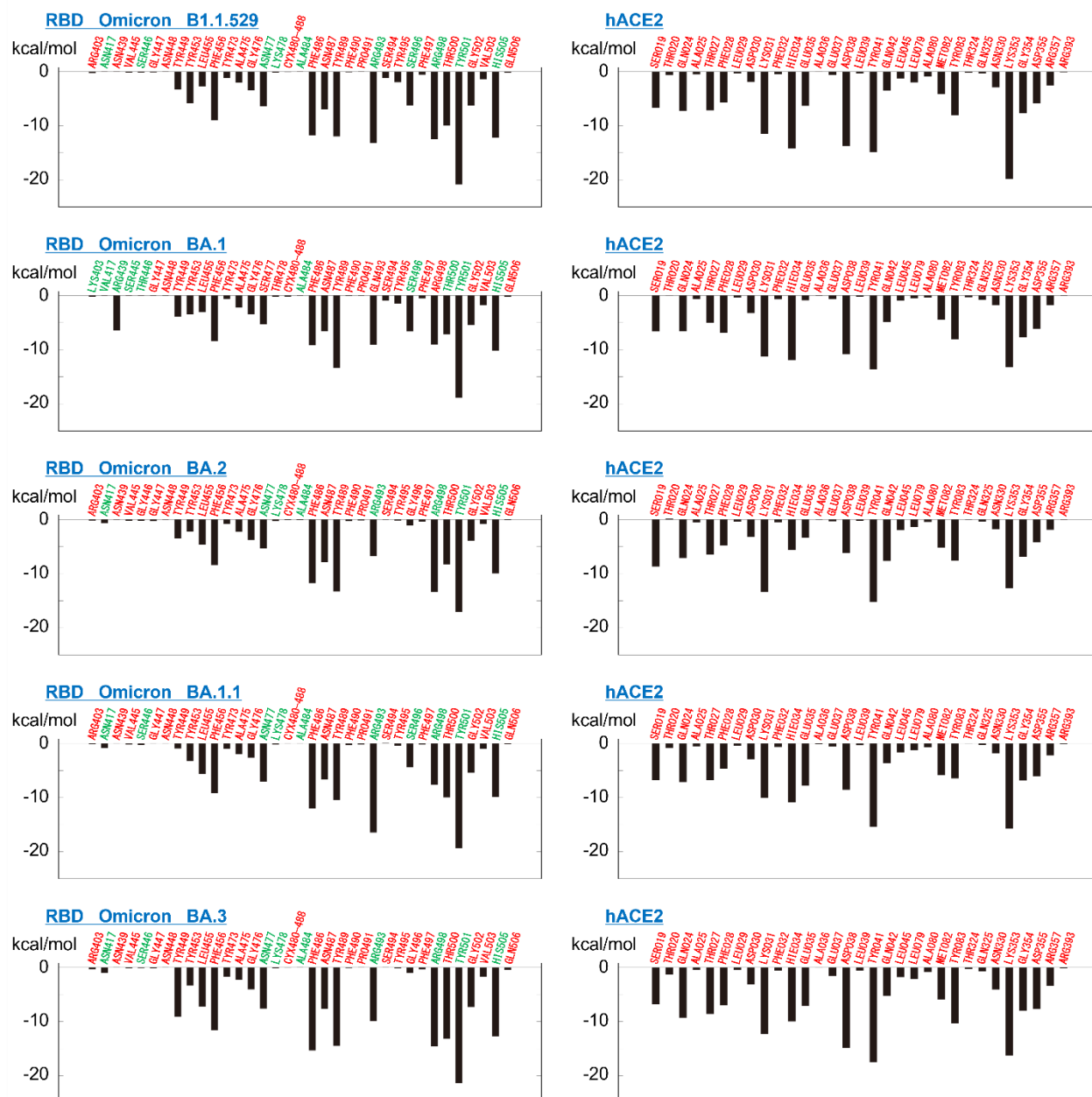


Figure S9 (continue)

