Structural bases for the higher adherence to ACE2 conferred by the SARS-CoV-2 spike Q498Y substitution

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A remarkable amount of SARS-CoV-2 variants and other yet unmonitored lineages harbour amino acid substitutions with potential to modulate the interface between the spike receptor binding domain (RBD) and its receptor ACE2. The naturally-occurring Q498Y substitution currently present in circulating SARS-CoV-2 variants has drawn the attention of several investigations [1-4], and recent studies have detected this substitution in previously unidentified SARS-CoV-2 lineages found in wastewater samples of New York City [5].

To decipher the structural bases that underlie the enhanced affinity attributed to this substitution, I have crystallized the RBD Q498Y mutant bound to its human ACE2 receptor. Compared to the structure with its wild type counterpart, the RBD Q498Y:ACE2 complex reveals conservation of major H-bond interactions and a more populated, non-polar set of contacts mediated by the bulky side chain of Tyr498, as well as one additional π-π stacking interaction, that collectively lead to this increase in the binding affinity.

Our studies contribute to a deeper understanding on the impact of a relevant mutation present in current SARS-CoV-2 circulating variants and which might lead to stronger host-pathogen interactions [6].

Figure 1. Comparison of the interatomic contacts between RBD and ACE2 in the wild-type and Q498Y structures.

[1] Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, Lu X, Zhang Y, Ma L, Gu W, Qu A, Xu J, Shi Z, Ling Z & Sun B. (2020). Cell. Mol. Immunol. 17, 621–630 doi: 10.1038/s41423-020-0458-z
[2] Capponi S, Wang S, Navarro E J & Bianco S. (2021). Eur. Phys. J. E. Soft Matter. 44, 123 doi: 10.1140/epje/s10189-021-00119-5
[3] Ahamad S, Kanipakam H & Gupta D. (2022). J. Biomol. Struct. Dyn. 40, 263–275 doi: 10.1080/07391102.2020.1811774
[4] Li Y, Zhang Z, Yang L, Lian X, Xie Y, Li S, Xin S, Cao P, Lu J. (2020) iScience. Jun 26;23(6):101160. doi: 10.1016/j.isci.2020.101160
[5] Smyth D S, Trujillo M, Gregory D A, Cheung K, Gao A, Graham M, Guan Y, Guldenpfennig C, Hoxie I, Kannoly S, Kubota N, Lyddon T D, Markman M, Rushford C, San K M, Sompanya G, Spagnolo F, Suarez R, Teixeiro E, Daniels M, Johnson M C & Dennehy J J. (2022). Nat. Commun. 13, 635. https://doi.org/10.1038/s41467-022-28246-3
[6] Erausquin E, Glaser F, Fernández-Recio J, López-Sagaseta J. (2022) Acta Cryst D. 78: 1156–1170. https://doi.org/10.1107/S2059798322007677