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Impact of new UK (B.1.1.7) SARS-Cov-2 variant on interacting with ACE2 and host immune response

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019 and has rapidly disseminated across the world, resulting in a spectrum of manifestations ranging from mild upper respiratory infection to acute respiratory distress syndrome (ARDS) and death (Hu et al., 2020; Paniri et al., 2020; Paniri et al., 2021). As of July 25, 2021, 194,645,694 confirmed cases with 4,171,983 deaths have been reported worldwide (https://www.worldometers.info/coronavirus, n.d.). Of note, this disease discrepancy might be explained by the nature of SARS-CoV-2 itself. On December 13, a new SARS-CoV-2 variant named VUI-202012/01 (also known as B.1.1.7 or alpha variant according to WHO nomenclature), containing 17 mutations has been reported in the UK and it quickly spread in London and South East England (https://www.who.int/csr/don/21-december-2020-sars-cov2-variant-united-kingdom/en/, n.d.) (Table 1). Among the mutations, N501Y is located in the spike (S) protein, and is expected to change the three-dimensional structure of the S protein and raise the transmissibility of B.1.1.7 due to its importance in interaction with angiotensin-converting enzyme 2 (ACE2) and cell entry in comparison with other SARS-CoV-2 variants (https://www.who.int/csr/don/21-december-2020-sars-cov2-variant-united-kingdom/en/, n.d.). Studies are ongoing to elucidate possible association of B.1.1.7 mutations with alterations in virus entry, severity of symptoms, and vaccine response. Recent studies have shown that the B.1.1.7 variant is more virulent and there are concerns about vaccine efficacy on this variant. Owing to discrepancy concerning the impacts of mutations in the B.1.1.7 variant on transmissibility, antibody response, and vaccine efficiency, *in silico* studies on this new strain may shed some light on these issues (Leung et al., 2021; Collier et al., 2021; Wang et al., 2021; Volz et al., 2021).

Two molecular docking databases including HADDOCK (https://wenmr.science.uu.nl/haddock2.4/) and HDOCK (http://hdock.phys.hust.edu.cn/) were used to analyze the binding affinity of the S protein of three SARS-CoV-2 variants, the original Wuhan strain, the SARS-CoV-2 D614G mutant, and the VUI-202012/01 variant for ACE2 and transmembrane protease serine 2 (TMPRSS2). Interestingly, molecular docking results achieved with both tools have suggested that VUI-202012/01 can bind to ACE2 with higher affinity in comparison with the two other variants, and may increase cell entry capacity and transmissibility of the new variant of SARS-CoV-2 (Table 1). Accordingly, Ramanathan et al. have shown that the B.1.1.7 variant harboring the N501Y mutation show a two-fold stronger binding affinity to ACE2in comparison with SARS-CoV-2. Interestingly, it has also been demonstrated that the B.1.351 variant first detected in South Africa and carrying three mutations (E484K, N501Y, and K417N) binds to ACE2 with a five times stronger affinity than SARS-CoV-2 (Ramanathan et al., 2021). Furthermore, *in silico* investigation by Villoutreix et al. has revealed that N501Y (identified in both the UK and South African strains) influence Spike-ACE2 interaction, and consequently increases transmissibility and possibly its pathogenicity while the K417N and E484K substitutions (South African strain) showed no significant impact (Villoutreix et al., 2021). Consistently, *in silico* analysis of ACE2-S protein interaction conducted by Singh et al. and Ortega et al. have revealed that N501Y might raise the affinity of S protein with host receptor (Ortega et al., 2021; Singh et al., 2021).

It is interesting to mention that Calcagnile et al. have reported that ACE2 missense variant K26R shows increased affinity for SARS-CoV-2 Spike protein which is more common in European and American populations (Calcagnile et al., 2021). Furthermore, bioinformatics and structural approaches analysis conducted by Spratt et al. have shown that D614G in Spike protein and P323L in RNA polymerase which are present in new variants may increase SARS-CoV-2's infectivity in comparison with SARS-CoV variant (Spratt et al., 2021). Nonetheless, results from interaction studies between TMPRSS2 and S protein showed no significant difference among the three SARS-CoV-2 variants (Table 2 and Fig. 1).

Strikingly, analyses of protein epitopes using the Immune Epitope Database (IEBD) (https://www.iedb.org/) has revealed a significant difference between epitope profiles of the original Wuhan strain, the SARS-CoV-2 D614G mutant, and the B.1.1.7 variant (Table 2). It has been shown that B.1.1.7 has 409 unique epitopes with high prediction score that are identified by specific antigen-presenting cells containing

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Table 1
Non-synonymous and deletion mutations identified in B.1.1.7.

Gene	Nucleotide	Amino acid
ORF1ab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 del
	21765-21770 deletion	HV 69-70 del
	21991-21993 deletion	Y144 del
Spike	A23063T	N501Y
	C23271A	A570D
	C237604A	P681H
	C23709A	T716I
	T24506G	S982A
	G24914C	D1118H
ORF 8	C27972T	Q27stop
	G28048T	R52I
	A28111G	Y73C
N	28280 GAT-> CTA	D3L
	C28977T	S235F

ORF: Open reading frame; N: Nucleoprotein.

Table 2
Comparison of S protein-ACE2 docking of SARS-CoV-2, G variant, and B.1.1.7.

		SARS-CoV-2	D614G mutant	B.1.1.7variant
HADDOCK 2.4	HADDOCK score	−62.7 +/− 10.5	−71.5 +/− 2.6	−94.1 +/− 14.0
	RMSD from the overall lowest-energy structure	9.1 +/− 2.0	23.9 +/− 0.4	4.5 +/− 0.1
	Van der Waals energy	−73.7 +/− 2.7	−73.3 +/− 3.1	−98.0 +/− 4.1
	Electrostatic energy	−180.3 +/− 30.2	−218.1 +/− 46.8	−244.6 +/− 30.8
	Desolvation energy	−17.4 +/− 6.5	−13.4 +/− 2.3	−7.6 +/− 4.5
	Restraints violation energy	645.8 +/− 80.0	589.0 +/− 62.7	603.6 +/− 57.1
	Buried Surface Area	2039.2 +/− 112.6	2123.2 +/− 23.4	2939.7 +/− 141.9
	Z-Score	−0.9	−1.2	−1.6
HDOCK	Docking Score (ACE2)	−311.01	−298.48	−358.28
	Docking Score (TMPRSS2)	−279.02	−279.02	−283.33
IEDB	MHC I	Total epitopes: 152		Total epitopes: 146
		VLNDILSRL		
		IPTNFTISV		VLNDILARL
		SPRRARSVA		IPINFTISV
		GVYYHKNNK		LQSYGFQPTY
		IAIPTNFTI		QSYGFQPTY
		QTNSPRRAR		IAIPINFTI
		YYHKNNKSW		QTQTNSHRR
		SVLNDILSR		
	MHC II	Total epitopes: 8		Total epitopes: 6
		IPTNFTISVTTEIL		IPTNFTISVTTEIL
		PTNFTISVTTEIL		PTNFTISVTTEIL
		AIPTNFTISVTTEI		AIPTNFTISVTTEI
		AIPTNFTISVTTEIL		AIPTNFTISVTTEIL
		TNFTISVTTEILPV		TNFTISVTTEILPV
		IPTNFTISVTTEI		IPTNFTISVTTEI
		IAIPTNFTISVTTEI		IAIPTNFTISVTTEI
		TNFTISVTTEIL		TNFTISVTTEIL
		PTNFTISVTTEILP		PTNFTISVTTEILP
		TNFTISVTTEILP		TNFTISVTTEILP

MHC-II while these epitopes have not been found in SARS-CoV-2 and D614G strain. On the other hand, 6 specific epitopes were detected for B.1.1.7 that might be identified by cells containing MHC-I in comparison with SARS-CoV-2 and D614G strain. Surprisingly, IEBD has also shown that 4 of 17 B.1.1.7 mutations including N501Y, A570D, T716I, and D1118H are located in epitopes that may be identified by antibodies, and consequently hosts might show a different response to this new variant in comparison with the two other COVID-19 variants. Interestingly, further analysis by PHYRE2 (http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index) has indicated that N501 has a low conservation score, and is sensitive to mutations as we see in the B.1.1.7 S protein (N501Y). Furthermore, ligand binding site investigated by ITASSER (https://zhanglab.ccmb.med.umich.edu/I-TASSER/) has revealed a significant change in ligand binding site of the B.1.1.7 S protein (874, 877, 878) in comparison with D614G variant (294, 297, 298, 301) highlighting the possible impact of new mutations on interaction of the B.1.1.7 S protein with different cell receptors, SARS-CoV-2 virulence, and host immune responses. Collectively, our molecular docking results suggest that B.1.1.7 might bind more tightly to ACE2, and may therefore become more virulent. Although, there is a

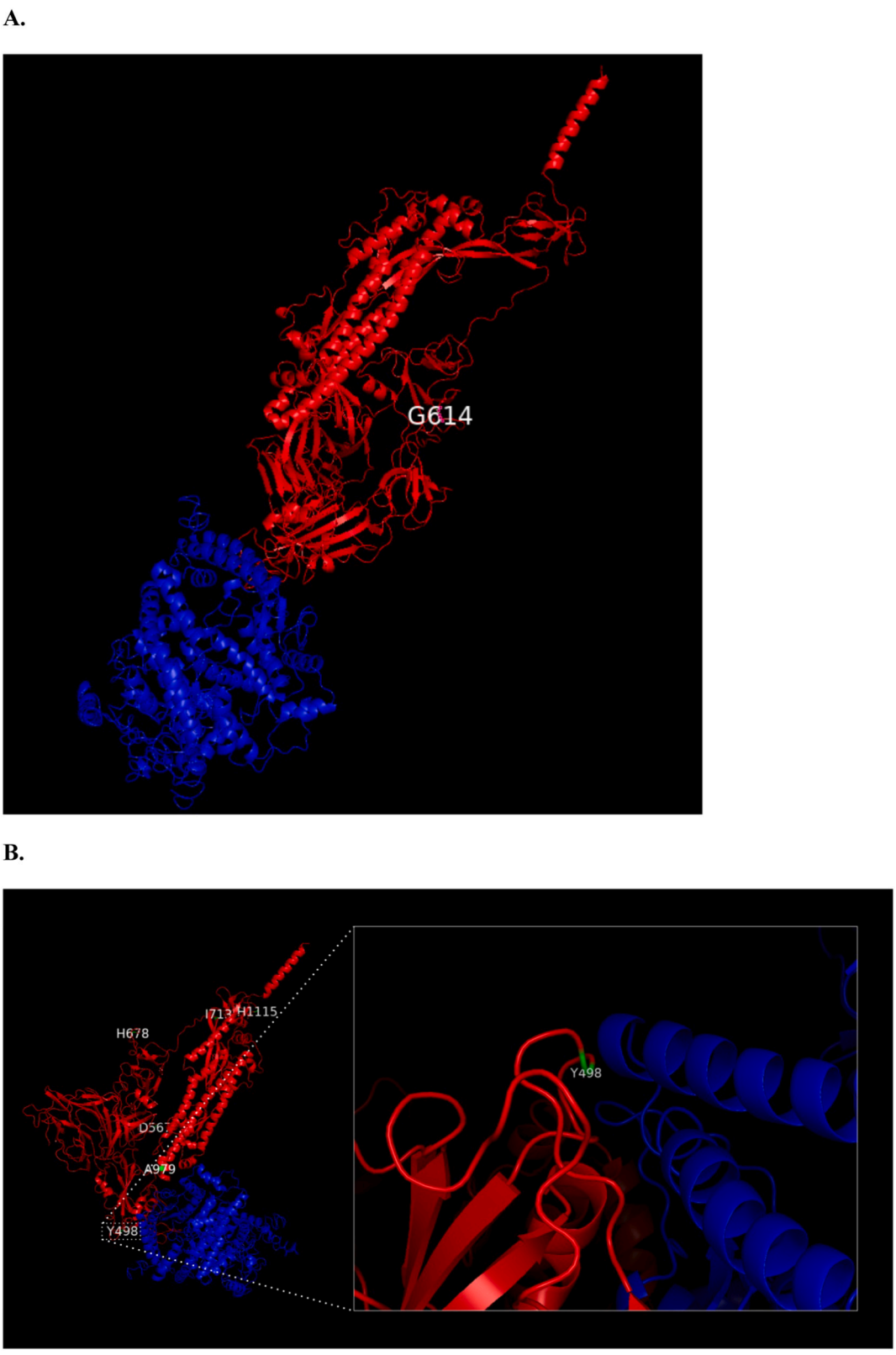

Fig. 1. Docking structure of ACE2 binding with spike protein fragment. **(A)** D614G variant; **(B)** B.1.1.7. HADDOCK have shown that glycine at position 614 is not involved in S protein-ACE2 interaction in the D614G variant. Moreover, it revealed that N501Y strongly contributes to the S protein-ACE2 interaction in the B.1.1.7 variant.

discrepancy about the rate of transmissibility of the B.1.1.7 variant, evidence thoroughly show that the B.1.1.7 variant is more virulent and there are concerns about vaccine efficacy on this variant (Leung et al., 2021; Collier et al., 2021; Wang et al., 2021; Volz et al., 2021; Muik et al., 2021).

Therefore, given the high mutation rate of SARS-COV-2, more studies need to be performed to fully elucidate the efficiency of vaccines, and thereby updating vaccines may be considered according to new variants.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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