

tive cleavage by furin and other proteases". Such an S1-S2 cleavage site is not observed in all related viruses belonging to the subgenus Sarbecovirus, except for a similar three amino acid insertion (PAA) in RmYN02, a bat-derived coronavirus newly reported from *Rhinolophus malayanus* in China" (FIG. 3a). Although the insertion in RmYN02 does not functionally represent a polybasic cleavage site, it provides support for the notion that this characteristic, initially considered unique to SARS-CoV-2, has been acquired naturally'. A structural study suggested that the furin-cleavage site can reduce the stability of SARS-CoV-2 S protein and facilitate the conformational adaption that is required for the binding of the RBD to its receptor". Whether the higher transmissibility of SARS-CoV-2 compared with SARS-CoV is a gain of function associated with acquisition of the furin-like cleavage site is yet to be demonstrated". An additional distinction is the accessory gene orf8 of SARS-CoV-2, which encodes a novel protein showing only 40% amino acid identity to ORF8 of SARS-CoV. Unlike in SARS-CoV, this new ORF8 protein does not contain a motif that triggers intracellular stress pathways". Notably, a SARS-CoV-2 variant with a 382-nucleotide deletion covering the whole of ORF8 has been discovered in a number of patients in Singapore, which resembles the 29- or 415-nucleotide deletions in the ORF8 region observed in human SARS-CoV variants from the late phase of the 2002-2003 outbreak". Such ORF8 deletion may be indicative of human adaptation after cross-species transmission from an animal host. m. ... Py, ae: fF age. yp aane