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THE STRAIN OF
SARS-COV-2

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SARS-CoV-2 is the third documented spill over of an animal coronavirus to humans in the last two decades. There is an enormous number of viruses circulating in the environment which have never been fully characterised. The genome sequence is all that is known for the majority of these viruses and it is on this basis that viruses are named¹.

Evolution

The SARS-CoV and MERS-CoV pathogens are zoonotic in origin – both deriving from bats as the animal host source, and mask palm civets and camels to be the intermediate animal hosts (between bats and humans), respectively². Recent reports suggest SARS-CoV-2 is 96 per cent identical at the genome level to previously detected bat coronaviruses, which belongs to the SARS-related coronavirus species. Although bats could be the original host for SARS-CoV-2 also, the virus may initially have been transmitted to an intermediate animal host at the Wuhan Huanan Seafood Wholesale Market².

Given the similarity of SARS-CoV-2 to bat SARS-CoV-like coronaviruses, it is likely that bats also serve as reservoir hosts for its progenitor². Although RaTG13, sampled from a *Rhinolophus affinis* bat, is approximately 96 per cent identical overall to SARS-CoV-2, its spike diverges in the receptor binding domain (RBD), which suggests that it may not bind efficiently to human ACE2 (refer previous Covid fact sheet). Malayan pangolins (*Manis javanica*) illegally imported into Guangdong province contain coronaviruses similar to SARS-CoV-2. Some pangolin coronaviruses exhibit strong similarity to SARS-CoV-2 in the RBD, including all six key RBD residues. This strongly suggests that the SARS-CoV-2 spike protein optimised for binding to human-like ACE2 is the result of natural selection³.

In such situations where a virus jumps from one animal host to another species—which is probably how this coronavirus initially infected humans—most mutations are detrimental to or have no effect on the virus, and selection pressure may improve survival in the new host. Therefore, we predict that one or more mutations may be selected and sustained during the 2019-nCoV outbreak as the virus adapts to human hosts and possibly changes virulence⁴, as reported in the previous study. Thus mutation can be both useful or destructive for the virus over time, but also may be structurally/functional silent⁵.

The host clearly exerts evolutionary pressures in virus mutation⁶. In SARS-CoV, there was positive selection during interspecies transmission events (from civets to humans) with rapid adaptation and mutation at the receptor binding domain of the S protein. The receptor binding domain of SARS-CoV is capable of recognising the ACE2 receptors of various animals – but key mutations increase the affinity of the interaction of the spike protein of the RBD with human ACE2 receptor i.e. these mutations are critical to viral adaptation to humans⁶.

Varying mutations with dubious significance

When genomic datasets from COVID-19 virus isolated in China, Thailand, and the USA were analysed, increasing genetic divergence of SARS-CoV-2 in human hosts was noted². RNA viruses have a high mutation rate due to the lack of proofreading activity of polymerases^{6,7}. Consequently, RNA viruses are prone to evolve resistance to drugs and escape from immune surveillance.

The mutation rate of SARS-CoV-2 is still unclear, but is believed to be slightly lower than SARS-CoV (0.80-2.38 x 10⁻³ nucleotide substitutions per site per year)⁷.



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This mutation rate also results in high levels of intra-host variants. The median number in a recent trial was found to be 4 (range 0 to 51), which is similar to Ebola. Although the authors did not find any mutation hotspot genes in either polymorphism or intrahost variants, the observation of shared intra-host variants among different individuals implied the possibility of adaptive evolution of the virus in patients, which could potentially affect the antigenicity, virulence, and infectivity of the virus⁷. By investigating a person-to-person spread event between two members of the one household, however, there was no evidence found for transmission of intra-host variants⁷.

In another study analysing genetic variants among 95 complete sequences, there was a strong association between the time of sample collection, location of sample, and accumulation of genetic diversity. 116 mutations were found, with unknown functional consequence⁸.

Li et al reported there were three phylogenetic clusters and three transmission clusters when the genetic distance between the 2019-nCoV strains was less than 0.001 per cent substitutions/site². This identification of three central variants has been replicated⁹, distinguished by amino acid changes – named A, B and C. A is the ancestral type according to the bat outgroup coronavirus. The A and C types are found in significant proportions outside East Asia i.e. Europe and the Americas, but the B type is most common in East Asia. The B type ancestral genome appears not to have spread outside East Asia without first mutating into derived B types, pointing to founder effects or immunological/environmental resistance against this type outside Asia⁹ i.e. it must first mutate to overcome resistance outside East Asia.

An earlier study found many mutations and deletions on coding and non-coding regions

of SARS-CoV-2.11. Of note, three mutations (D354, Y364, and F367) located in the spike surface glycoprotein receptor-binding domain. The spike surface glycoprotein plays an essential role in binding to receptors on the host cell and determines host tropism. It is also the major target of neutralising antibodies. Mutations in the spike surface glycoprotein might induce its conformational changes, which probably led to the changing antigenicity¹⁰.

Interpretation of genome-driven virus evolution has remained difficult because the published data still refer to a relatively low number of viral isolates. One group examined all available SRAS-CoV-2 sequence with the aim of mapping structural variations and the patterns for selection of viral protein genes⁵. Clustering of sequence presenting amino acidic mutations did not indicate a geographical/epidemiological link with the patients from whom SARS-CoV-2 was isolated⁵.

In particular, two key mutations were discovered affecting the non-structural protein 6 (NSP6) and the open reading frame 10 (ORF10). These authors went one step further, however, and examined the structure of the proteins encoded by the mutated genes in an attempt to gain some insight into the biologic significance. Amino acid change stability analysis suggests both mutations could confer lower stability of the protein structures⁵. In the case of the NSP6 mutation, it is hypothesised that the presence of the mutation produces several phenylalanine residues in the outer membrane region of the NSP6 and this favours the affinity between this region and the endoplasmic reticulum, thereby compromising the ability of autophagosomes to deliver viral components to lysosomes for degradation, thus conferring a possible viral advantage^{5,6}.



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Coronaviruses have a proof-reading exoribonuclease which checks against the high mutation rate in coronaviruses⁶. Deletion of this results in very high mutability and attenuation or even unviability. Interestingly, the nucleotide analogue, remdesivir, emerging as a potential therapeutic agent in SARS-CoV-2, is known to suppress replication through inhibition of this exoribonuclease and the RNA-dependent polymerase.

Conclusions

Compared to SARS-CoV, the mutation rate of SARS-CoV-2 is apparently lower, suggestive of a higher level of adaptation to humans⁶. This may have resulted from adaptation to another host close to humans⁶. Thus both viral factors, and the influence with the host as outlined above, are influential.

An increased level of viral diversity was found in some SARS-CoV-2 infected patients, suggesting that the virus has begun to adapt to the human environment and its genomes have begun to evolve in the population¹¹. While mutation is common, there still remains very high similarity between SARS-CoV-2 strains with few variable genomic regions¹².

This virus's comparative lower mutation rate (compared to SARS-CoV and Influenza) is perhaps related to its high infectivity i.e. it is not under any evolutionary pressure to evolve. This means, therefore, that it is perhaps less likely to spontaneously evolve into a more deadly variant. Supporting this hypothesis various scientific commentators have observed that the virus mutations don't seem to be any more infectious or fatal than the original strain that appeared in Wuhan, China, in late December.

There remains a very rare chance a virus could mutate to be more aggressive, but if anything, RNA viruses are more likely to mutate into a weaker version. Time and further study will tell ...

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