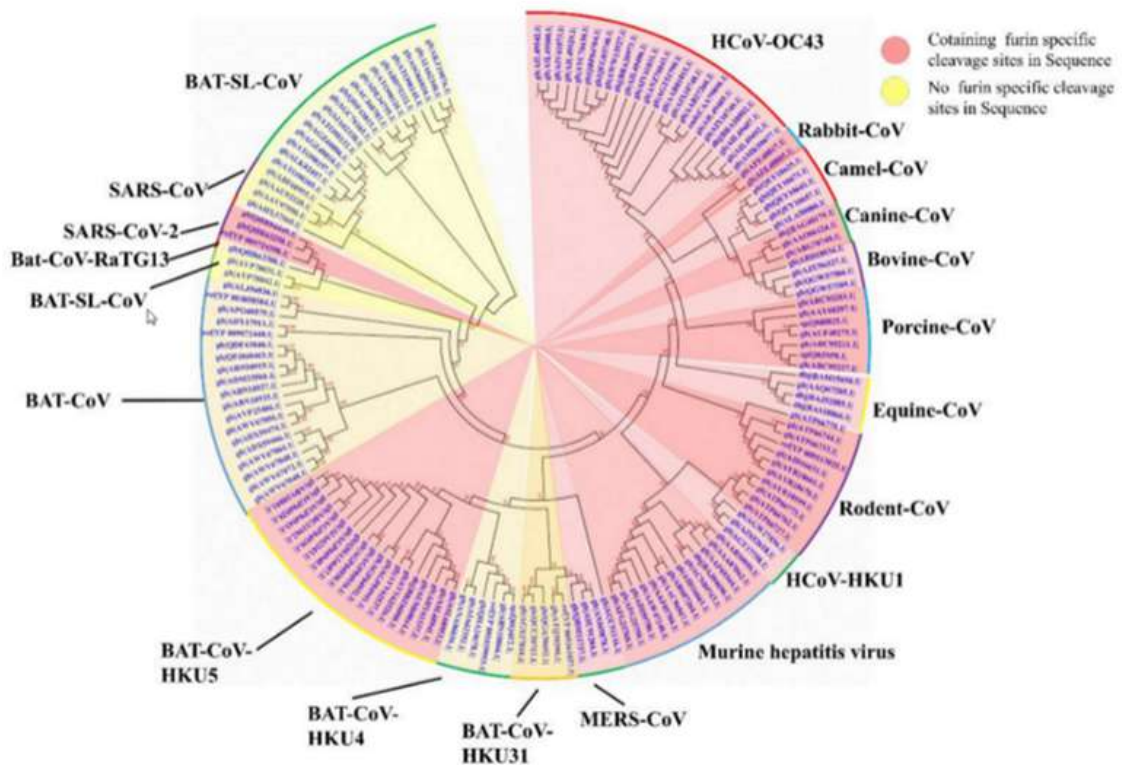


The furin cleavage site “RRAR” in SARS-CoV-2 is unique in its family, rendering by its unique insert of “PRRA”. *The furin cleavage site of SARS-CoV-2 is unlikely to have evolved from MERS, HCoV-HKU1, and so on.* From the currently available sequences in databases, it is difficult for us to find the source. Perhaps there are still many evolutionary intermediate sequences waiting to be discovered.

Here is a great illustration from the source article of the quote above. Coronaviruses with a furin site are marked in pink, 3 different strains of Cov2 are shown at 10 o'clock:



The closest relative with a furin site is the HKU5 strain, isolated by the Shi Zhengli team in 2014 in Guangzhou from bats of the genus Pipistrellus (added to [GenBank](#) in 2018). But it is a very distant relative — their spike proteins share only 36%.

So the virologists are puzzled. *Where did this 12 nucleotide insert come from? Could it be lab-made?* Well, virologists have studied furin sites in coronaviruses for decades, and have introduced many artificial ones in a lab.

For example, an American team had inserted RRSRR into the spike protein of the first SARS-CoV [back in 2006](#): *To investigate whether proteolytic cleavage at the basic amino acid residues, were it to occur, might facilitate cell-cell fusion activity, we mutated the wild-type SARS-CoV glycoprotein to construct a prototypic furin recognition site (RRSRR) at either position.*

| | | | |
|-----------|--------------------|--|--|
| | ◆667 | ◆672 | |
| wild-type | PIGAGICASYHTVSLLR | STSQKSIVAYTMSLGADSSIAYSNNTTIAIPTNFSISITTEVMPVS | |
| HTR | PIGAGICASYHTRRSRR | STSQKSIVAYTMSLGADSSIAYSNNTTIAIPTNFSISITTEVMPVS | |
| HTVR | PIGAGICASYHTVRRSRR | STSQKSIVAYTMSLGADSSIAYSNNTTIAIPTNFSISITTEVMPVS | |
| SLLR | PIGAGICASYHTVSLLR | SIVAYTMSLGADSSIAYSNNTTIAIPTNFSISITTEVMPVS | |

And the Japanese [have inserted a similar site](#) (RRKR) into the SARS-CoV protein in 2008, though a bit downstream than in CoV2: