...Evidence Of Genetic Engineering In Sars-Cov-2 Part 6: Stretchy Sticky Sugar Loops In January 2020, When Hiv Researchers (Pradhan Et Al) Identified Inserts From Hiv In Sars-Cov-2 Genome They Were Met

English

0 Comment

Dog'S Breakfast

Evidence of Genetic Engineering in SARS-COV-2 Part 6: Stretchy Sticky Sugar Loops

In January 2020, when HIV researchers (Pradhan et al) identified inserts from HIV in SARS-COV-2 genome they were met with immediate criticism. Fauci called it "outlandish"

sundayguardianlive.com/news/fauci-des...

Most of the criticism was based on undisputable facts:

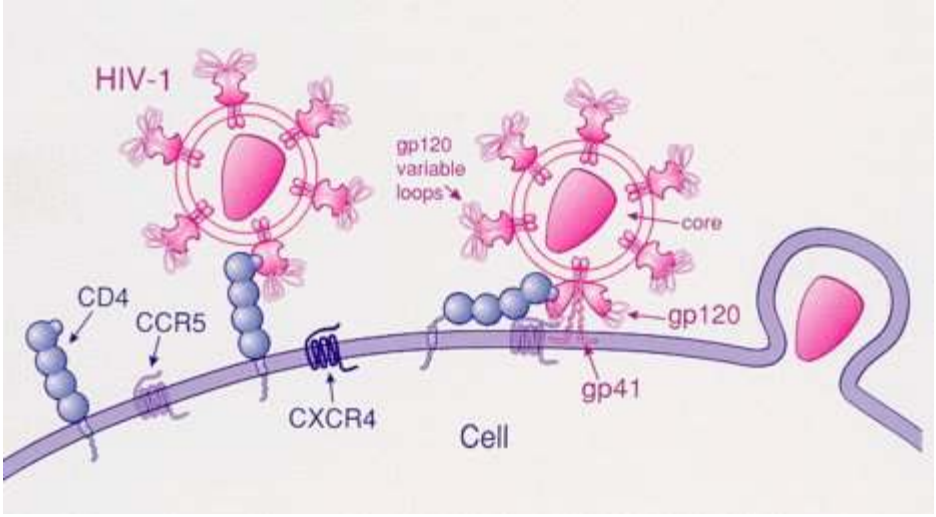
-the “inserts” are short, a few amino acids that might have occurred randomly
-they aren’t found in all HIV genomes, the regions they’re found in are highly variable
-and then RaTG13 came along…

asia.nikkei.com/Spotlight/Caix…

> However, three of the inserts mentioned in the paper were found in a known coronavirus carried by bats, and the fourth was very similar to the bat coronavirus, Yang said. None of them is from the HIV, Yang said.
>
> Yang added that the so-called inserts exist in the genetic sequences in many other animals and plants. The paper listed only seven to 12 amino acid residues of the inserts, while the HIV contains hundreds of amino acid residues. If such inserts can be compared with a fragment of the HIV, similarities can also be found in the genetic sequences of a variety of organisms, such as fruit flies, mold or even lentils, Yang wrote.

Should we accept RaTG13 at face value? A sequence “found” by WIV’s Zhengli Shi, as suspicion was turning to her? A sequence that explains strange features unseen before SARS-COV-2? Of an isolate that doesn’t exist? Questions for later.
First let’s discuss the other criticisms…

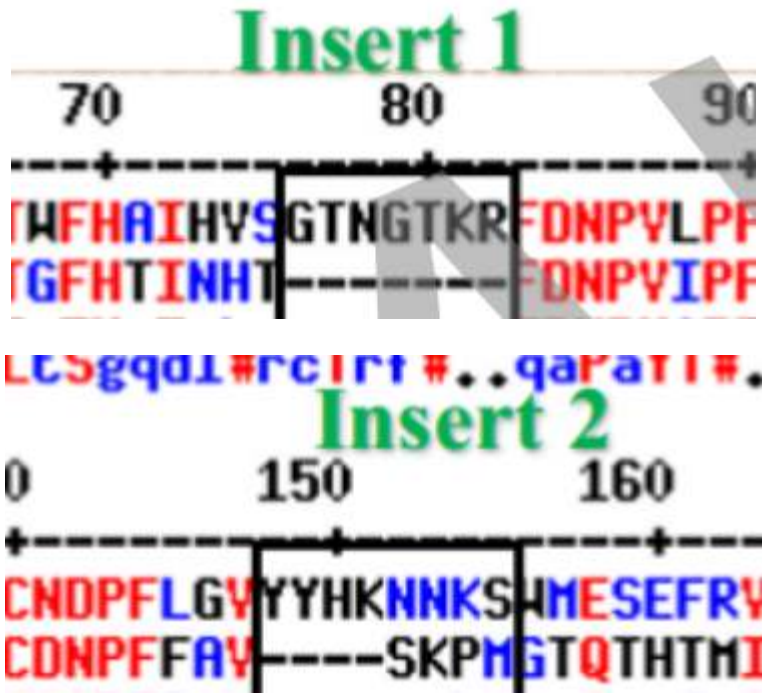
HIV-1 is structurally quite similar to a coronavirus. The CoV spike (S) is analogous to HIV’s Env, and its protein product gp160. Gp160 splits into two parts (gp41/gp120) much as S splits into S1/S2. HIV’s main receptor is CD4, rather than ACE2 for SARS



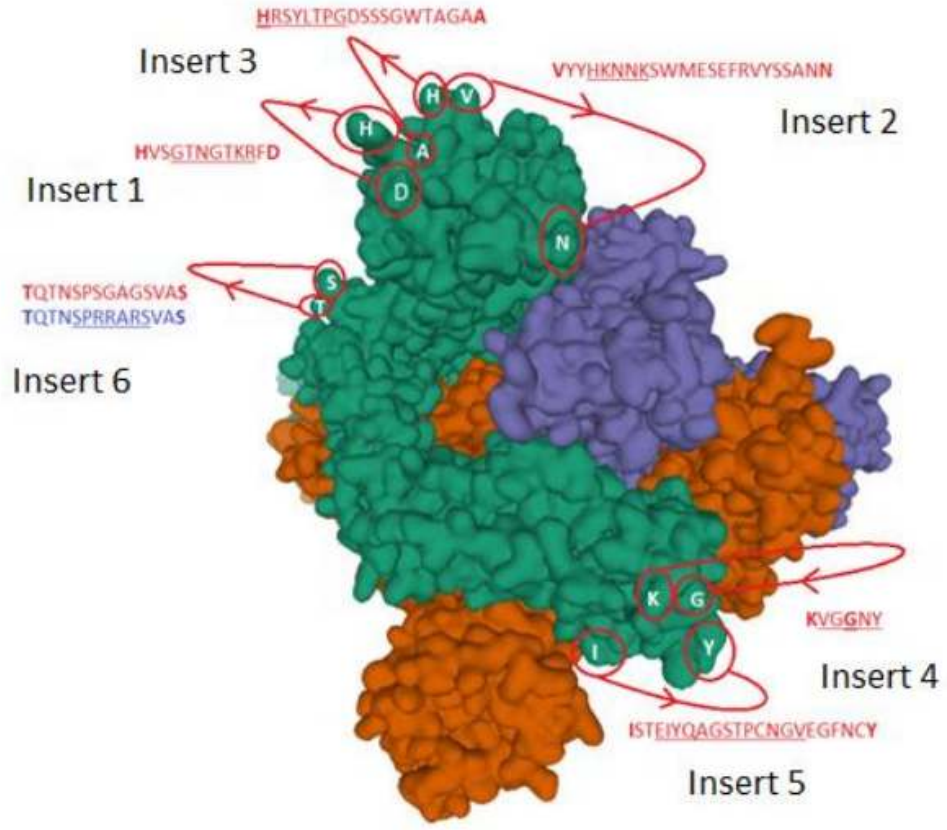
Gp120 consists of 5 conserved regions interspersed with 5 variable loops (V1, V2...V5) which are flexible, and vary in length and sequence between genomes and over the course of infection (which is long in HIV). These loops are the source of the inserts found by Pradhan et al.

Motifs	Virus Glycoprotein	Motif Alignment	HIV protein and Variable region	HIV Genome Source Country/ subtype	Number of Polar Residues	Total Charge	pI Value
Insert 1	2019- nCoV (GP) HIV1(GP120)	71 76 TNGTKR TNGTKR 404 409	gp120-V4	Thailand */ CRF01_AE	5 5	2 2	11 11
Insert 2	2019- nCoV (GP) HIV1(GP120)	145 150 HKNNKS HKNNKS 462 467	gp120-V5	Kenya*/ G	6 6	2 2	10 10
Insert 3	2019- nCoV (GP) HIV1(GP120)	245 256 RSYL----TPGDSSSG RTYLFNETRGNSSSG 136 150	gp120-V1	India*/C	8 10	2 1	10.84 8.75
Insert 4	2019- nCoV (Poly P) HIV1(gag)	676 684 QTNS----------PRRA QTNSSILMQRSNFKG PRRA 366 384	Gag	India*/C	6 12	2 4	12.00 12.30

One thing that makes it less likely these sequences occurred by random co-incidence in SARS-COV-2 is that they are also found in similar structural positions, i.e. in flexible loops on the surface of the spike. In other sarbecovs known before 2020 these loops are much shorter.



Sorenson and Dalgleish independently identified these loops as suspect, though without making the connection to HIV. They pointed out the importance of the surface position and it's role enhancing pathogenesis, by increasing interactions with coreceptors
minervanett.no/files/2020/07/...

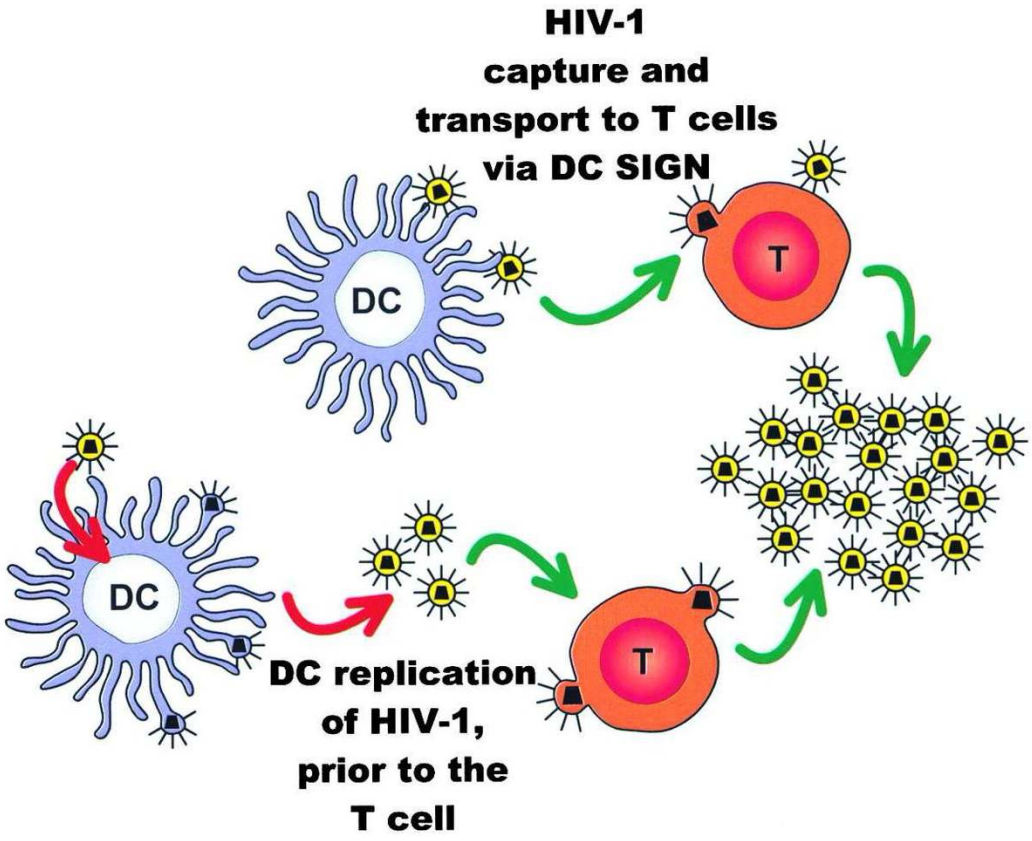


2. *The Spike displays new amino acid inserts with condensed cumulative charge, all of which are surface exposed (please refer to the reproduced figure from the vaccine paper, above).* This is a most significant finding as we mentioned in opening. Being physically located on the surface of the Spike protein greatly increases the infectivity and pathogenicity of the virus, enabling these inserts to participate in binding to co-receptors/negatively charged attachment receptors or even, as we have discovered, to the negatively charged phospholipid heads on the cell membrane. Such a result is typically the objective of gain of function experiments to create chimeric viruses of high potency. Therefore this is a strong indicator of manipulation

In HIV a common feature of the variable loops is that they contain glycosylation sites. This is where glycans (sugar molecules) from the host attach to the virus (green blobs in the animation). The virus uses these to try evade the immune system. https://twitter.com/i/status/1295725653720027136

The interaction between host and virus intermediated by the glycans is complex, part of an evolutionary contest. Some coreceptors on the host's cells also bind glycans and some viruses can exploit this.

In both HIV-1 and SARS, glycans on the virus were known to bind to receptors L-SIGN and DC-SIGN found on the surface of immune system dendritic cells. Instead of recognizing the virus as a pathogen, the dendritic cell transports it to a T-Cell which the virus can then infect.



Earlier SARS researchers had identified several glycosylation sites important for pathogenesis. Many of these are also found in SARS-COV-2 including 2 identified as critical for human infection. But the ones we're interested in aren't in SARS, only HIV.

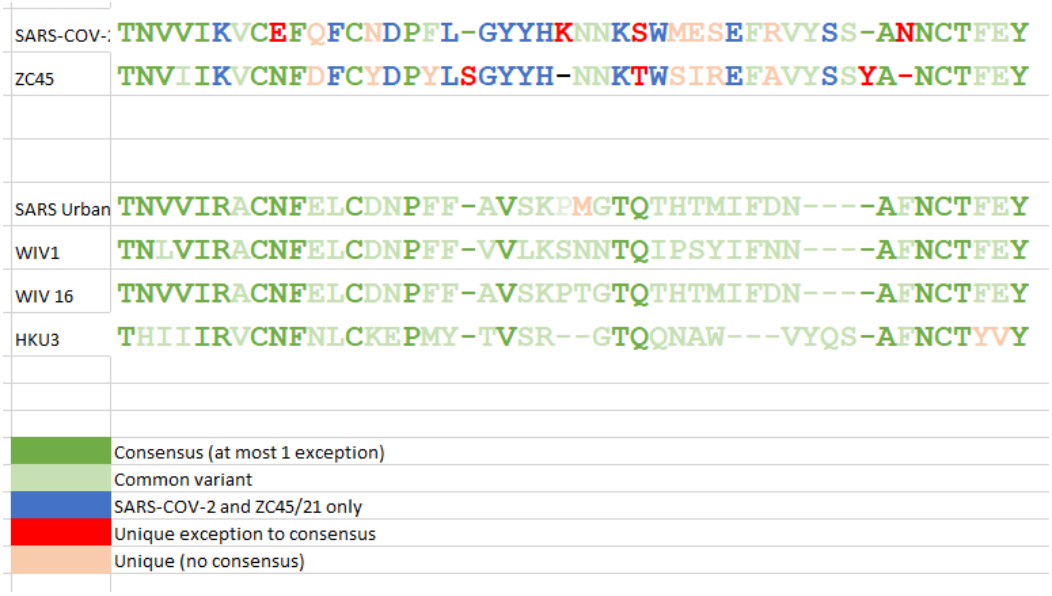
ncbi.nlm.nih.gov/pmc/articles/P...

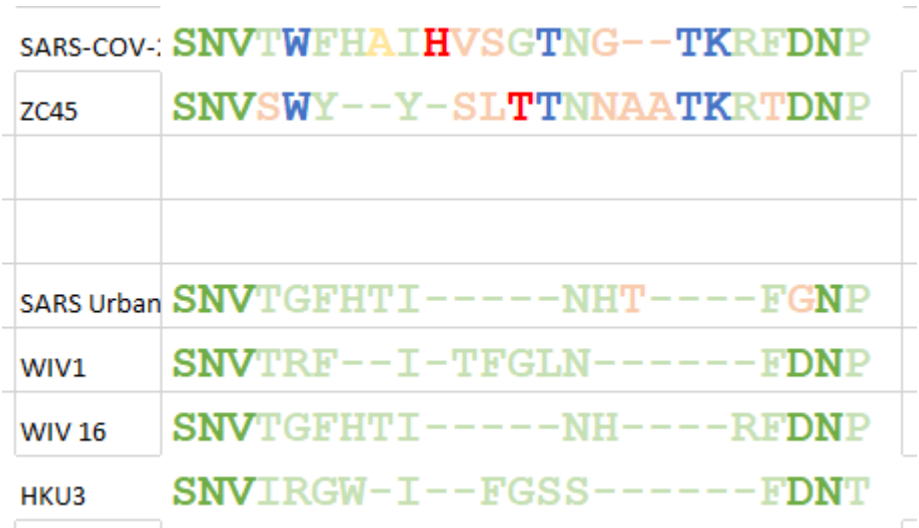
Specific Asparagine-Linked Glycosylation Sites Are Critical for DC-SIGN- and L-SIGN-Mediated Severe Acute Respiratory Syndrome Coronavirus Entry▿

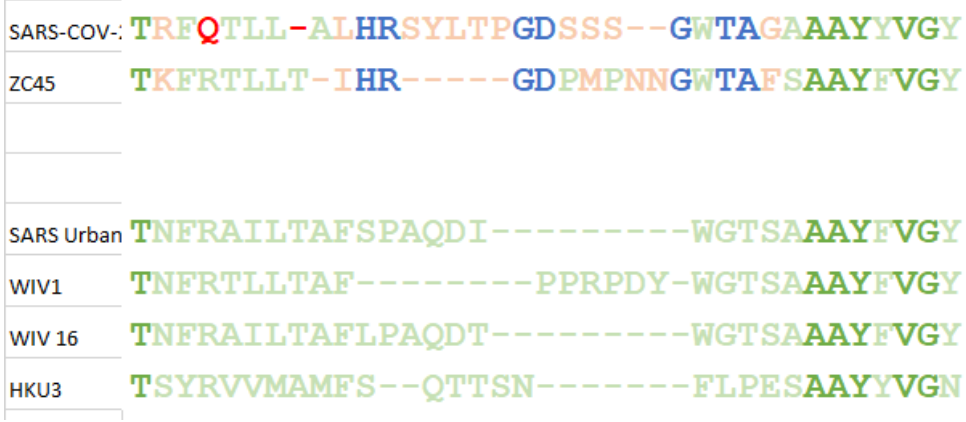
Dong P. Han,[1] Motashim Lohani,[1] and Michael W. Cho[1,2,3,*]

As expected, glycans on spike (S) glycoprotein are important for DC/L-SIGN-mediated virus infection. Site-directed mutagenesis analyses have identified seven glycosylation sites on the S protein critical for DC/L-SIGN-mediated virus entry. They include asparagine residues at amino acid positions 109, 118, 119, 158, 227, 589, and 699, which are distinct from residues of the ACE2-binding domain (amino acids 318 to 510). Amino acid sequence analyses of S proteins encoded by viruses isolated from animals and humans suggest that glycosylation sites N227 and N699 have facilitated zoonotic transmission.

Prior to SARS-COV-2 no sarbecovs had these extended loops (or they were much shorter). Aligning these regions with other sarbecov sequences known at the time there is little homology with any others – except one: ZC45 (and its close relative ZXC21), sequenced by China's PLA.

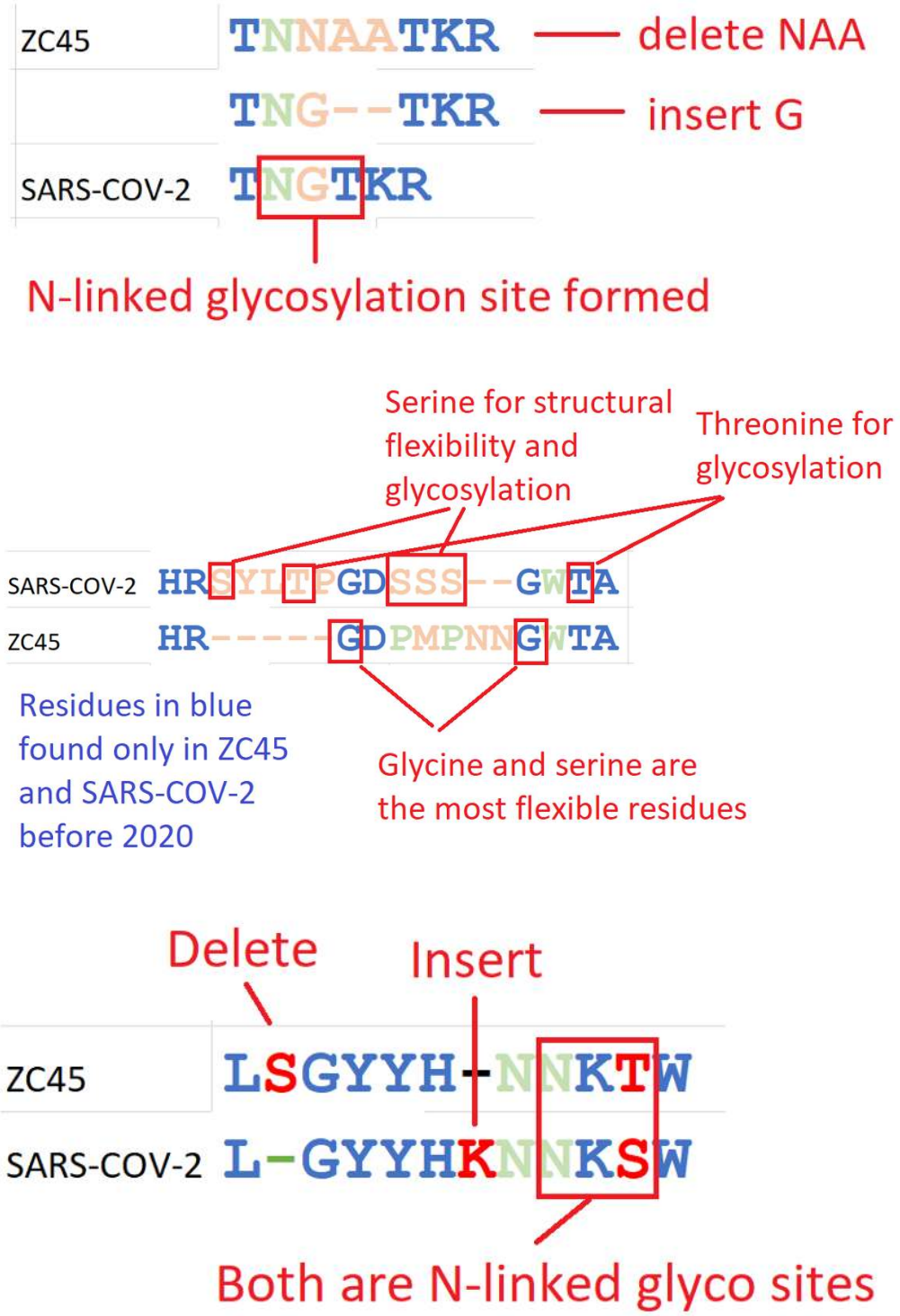






There are two types of glycosylation sites, N-linked and O-linked. An N-linked site consists of an Asparagine (N) followed by any amino acid, then a Serine (S) or Threonine (T). An O-linked site is simply any S or T (these are very common, but attract glycans less reliably).

We can see clear steps to engineer SARS-COV-2 from ZC45, unlike other sarbecovs (note the residues in blue are ONLY in ZC45/ZXC21). In genetic engineering G and S are often used to provide structural flexibility. These make it less critical to determine how a protein will fold.



Homology at these sites are a 3rd piece of evidence pointing to ZC45 being the precursor to SARS-COV-2 (others are a mutation in a conserved region of S2, and near the PALS1 binding motif in E protein). All may have been deduced from prior SARS research to increase pathogenicity.

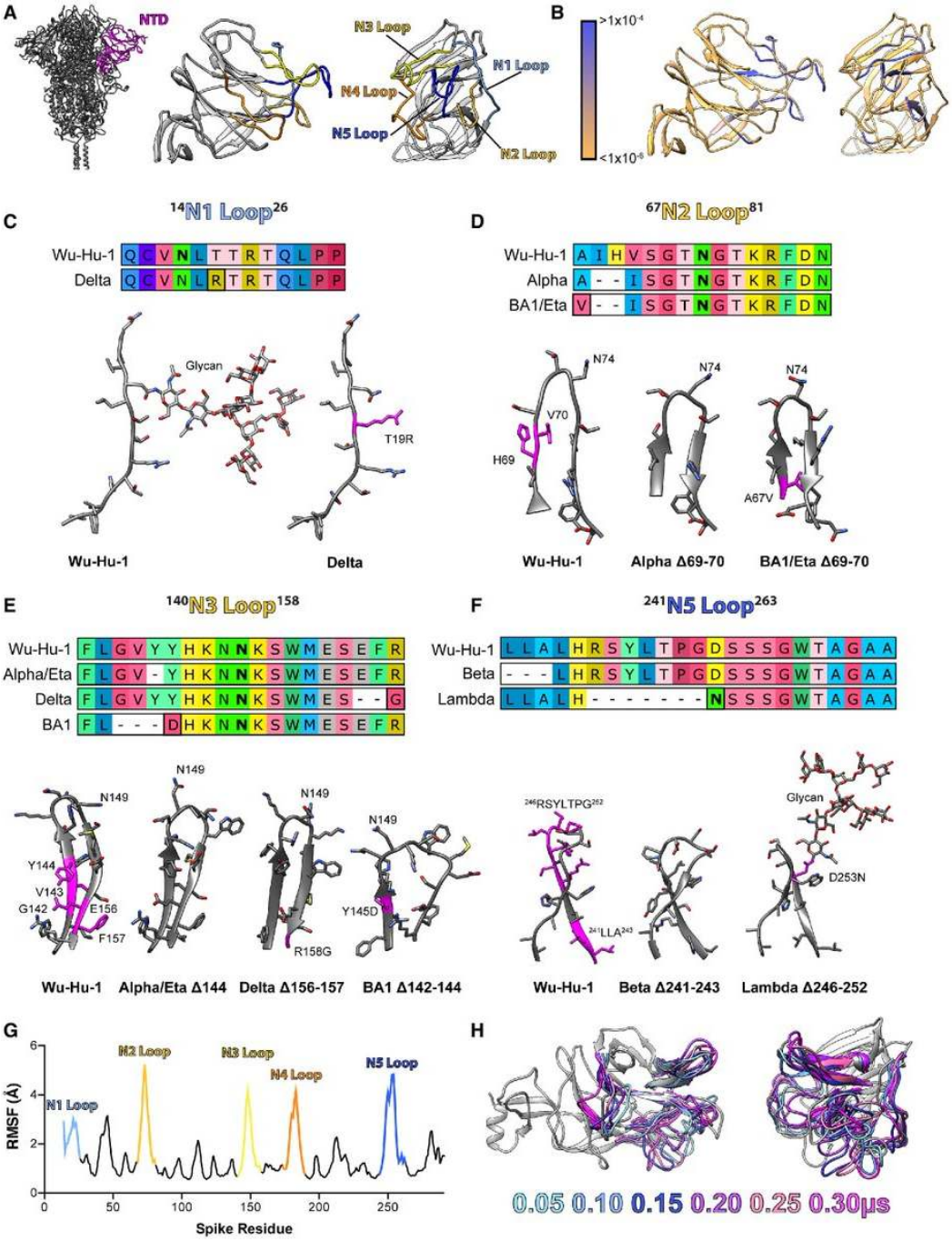
Starting with RatG13 many new sequences

(Pangolin CoVs, RMYN02, Cambodian CoVs, BANALs) have been “discovered” purporting to share similar features. But with what was known in January 2020, it might have been reasonable to think SARS-COV-2 was an engineered bioweapon.

In a future thread I’ll look at evidence that these newly discovered sequences may be fake, and problems for our understanding of evolution if they aren’t.
More on S2 and E protein mutations mentioned above:

https://twitter.com/breakfast_dogs/status/1473970400367362053?s=20&t=YDNlHt2KOZYatyLL-sZgjQ
https://twitter.com/breakfast_dogs/status/1545606228180893696?s=20&t=YDNlHt2KOZYatyLL-sZgjQ

A new paper out shows that some of these residues get deleted in recent SARS-COV-2 variants. This phenomenon is also common around the S1/S2 junction and FCD. This shows that engineers haven’t got everything right. Nature wants to revert to shorter loops.
embopress.org/doi/full/10.15...



The HKNNKS insert, here described as an antibody binding “supersite”, continues to evolve rapidly, creating new immune evasive mutants. https://twitter.com/EllingUlrich/status/1568194713110323203?s=20&t=OAMp8CkOcI1w57qXoDhq0g

Evidence Of Genetic Engineering In Sars-Cov-2: Part 8

Dog'S Breakfast

Evidence of Genetic Engineering in SARS-COV-2: Part 8.88 Mysteries of the Missing Link: ZC45 Among the first to raise the alarm to the new coronavirus spreading was an employee at Chinese biotech company Vision Medical. Her WeChat posts were translated and archived by DRASTIC.

Her story was later published in a @washingtonpost article, but a crucial detail. was omitted -that she had identified the closest viral sequences to the new virus as ZC45 and ZXC21, which had several crucial differences to other known SARS-like viruses.

图注：左上角一大块红色是SARS，边缘颜色没那么红的是Bat SARS like，再往外的大蓝边是另一群Bat SARS like，未知的病毒跟45、21聚在比较独立的一支上了，红框圈起来的。

比较奇怪的是，这个未知的病毒跟bat-SL-CoVZC45和bat-SL-CoVZXC21聚到了一个相对独立的分枝上，而其它Bat SARS like则很集中地聚在SRAS那一群里面，想着也许是这两个的分类有点问题，但去看了出处的文献，方法上跟其它的也没啥区别，尊重文献的分类吧，暂且认为是对的。（这也是后面某些专家们把这个未知病毒判定为新型冠状病毒的依据之一）

Legend: A large red block in the upper left corner is SARS, the edge colour that is not so red is for Bat SARS like, and the big blue border outside is another group of Bat SARS like, the unknown virus is clustered with 45 and 21 in a relatively independent branch up there, the red frame is circled.

It is strange that this unknown virus clustered with bat-SL-CoVZC45 and bat-SL-CoVZXC21 in a relatively independent branch, while other Bat SARS-like viruses were clustered in the SARS group. I thought that maybe there is a problem with the classification of these two. However, after reading the literature, there is no difference between the method and the others, so I respect the classification of the literature and I think that it is correct for the time being. (This is also one of the bases for some experts to later consider this unknown virus as a novel coronavirus)

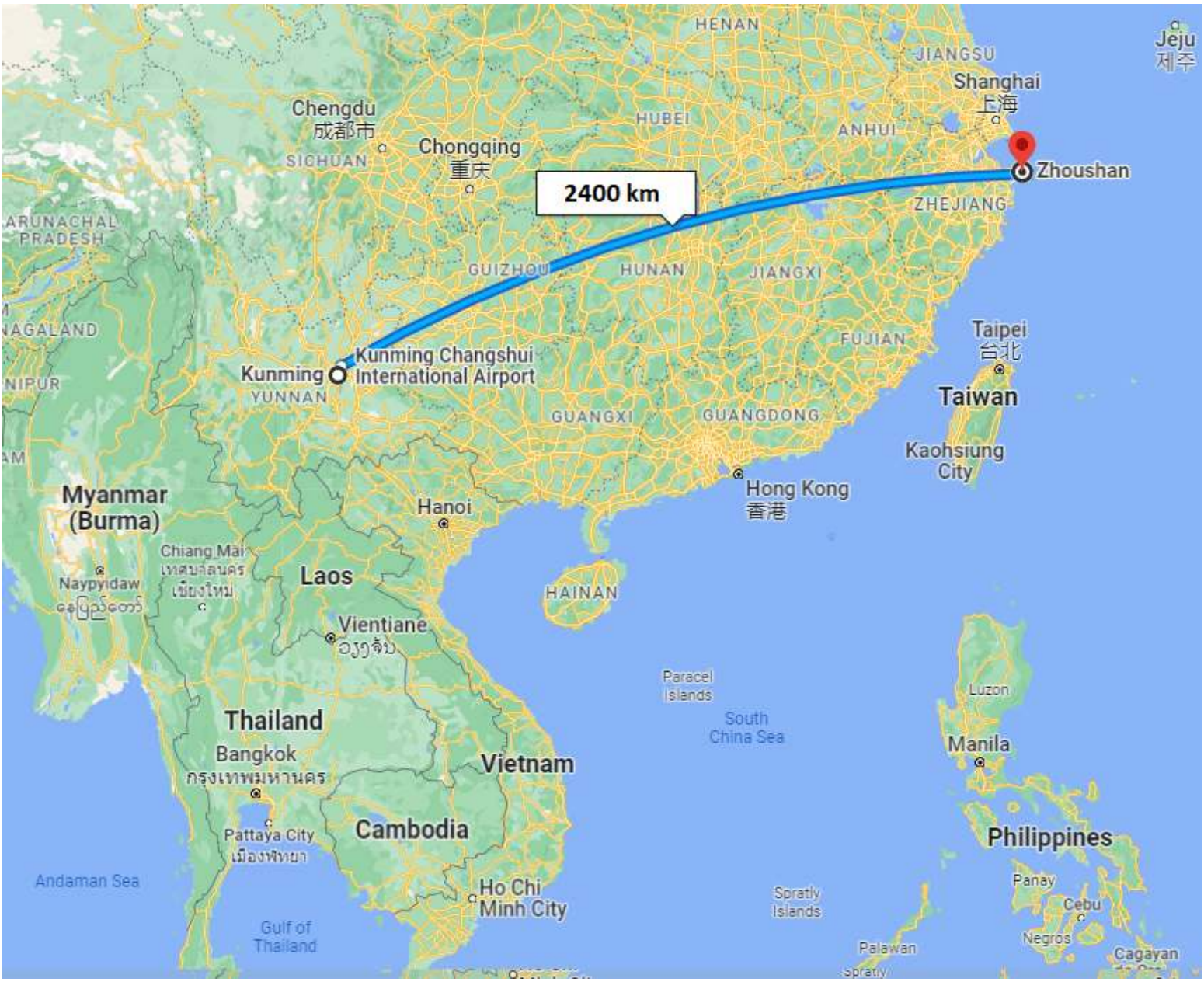
DRASTIC transcript

By afternoon, she had figured out that the novel virus was closely related to a pair of bat coronaviruses, similar to the SARS virus. By evening, she had created a phylogenetic tree, a diagram of viral evolution, showing how the virus closely resembled two other known bat coronaviruses.

How it was conveyed in Washington Post

ZC45* was found by a team led by the PLA's Nanjing Command, in Zhoushan, far from the hotspot for SARS-like viruses in SW China/SE Asia. They were able to infect mice, evidence of potential to jump species.

(*As ZXC21 is a close relative, I'll just refer to ZC45)



Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats

Dan Hu [1] [2], Changqiang Zhu [2], Lele Ai [2], Ting He [2], Yi Wang [3], Fuqiang Ye [2], Lu Yang [2], Chenxi Ding [2], Xuhui Zhu [2], Ruicheng Lv [2], Jin Zhu [2], Bachar Hassan [4], Youjun Feng [5], Weilong Tan [6], Changjun Wang [7] [8]

Affiliations – collapse

PLA Colonels

Previously 973 program scholar in US. Colleague of Shibo Jiang (New York Blood Center, Fudan University)

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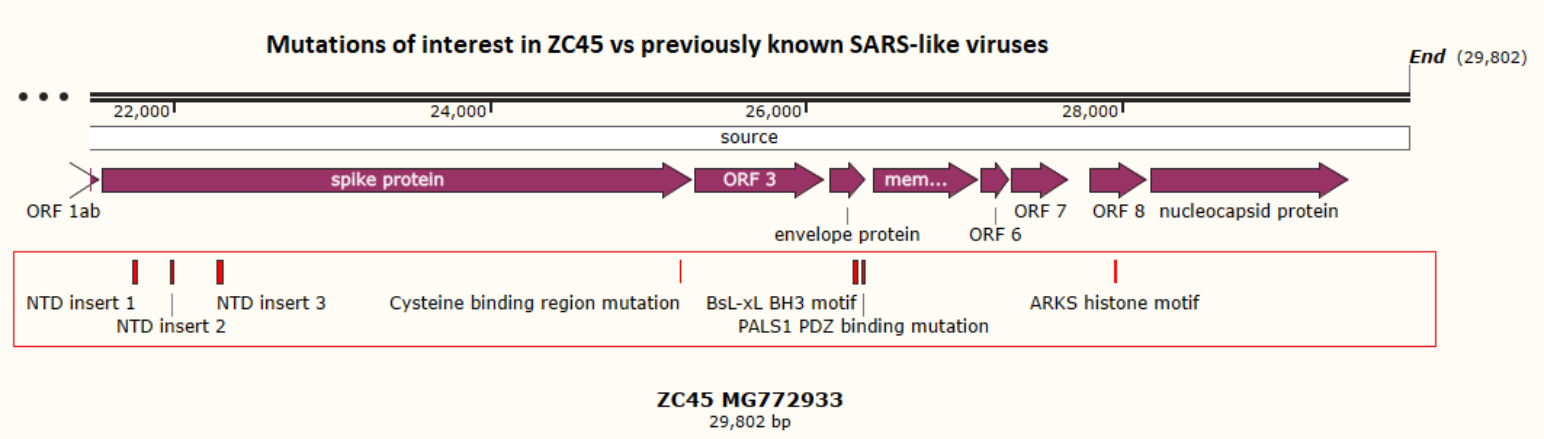
ZC45/ZXC21 discovery paper author affiliations

Prior to the pandemic ZC45 didn't receive much attention, perhaps because key mutations in the RBD indicating human infectivity weren't present. But elsewhere in the genome there are unique and potentially dangerous mutations, based on known mechanisms of pathogenicity in SARS1.



These mutations are

-mostly short, 1-2 amino acids changed in otherwise conserved regions
-in regions studied by SARS researchers and identified with pathogenicity
-also found in SARS-COV-2
-but NOT in SARS 1, or any other *previously published* SARS like sequences.

I highlighted *previously published* because there are now other sequences with these features. But let's put these aside for now as

-these weren't known prior to the pandemic
-they come from WIV, PLA or collaborators
-most only exist on paper, not claimed to exist as live virus

Instead let's apply a reasonable degree of skepticism. Let's assume if someone had started a global pandemic they may try cover up their involvement. That coverup may involve posting fake sequences, a simple task.

If we omit these doubtful sequences a troubling picture emerges

because
-ZC45 shares multiple unique mutations with SARS-COV-2
-These mutations are likely to make it more pathogenic
-ZC45 is a PLA virus

Since in Jan 2020 these other sequences didn't exist, it may have led some to suspect SARS-COV-2 is a PLA bioweapon, based on ZC45.

	Envelope (E) Protein	S2 "Cysteine rich region"
SARS-COV-2	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
Known Before SARS-COV-2 (Jan 2020)		
ZC45	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
ZC21	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGFCCKFDEDDSEPVLKGVKLHYT
SARS (Urbani)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018A	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rp/Shaanxi2011	MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSVGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4247	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018B	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
As6526	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4237	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Longquan-140	MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4081	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
BetaCoV/GX2013	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
HKU3-1	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2013	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs806/2006	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Cp/Yunnan2011	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs3367	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
WIV1	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018D	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4255	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs_672/2006	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
WIV16	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
RsSHC014	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
SARS (Civet)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs9401	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDPEPVLKGVKLHYT
Rs4084	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs7327	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Anlong-103	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
SC2018	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTIYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018C	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT

SITUATION IN Jan 2020 - OMG the new coronavirus has strange mutations only ever seen in viruses published by the PLA!!!

Clearly some scientists had these dark thoughts in Jan. But in Feb that abruptly changed. They accepted WIV's new paper bat cov RatG13, and later PLA's pangolin covs UNQUESTIONED as proof similar mutations exist in nature. Talk of an engineered virus became a "conspiracy theory".

From: Fauci, Anthony (NIH/NIAID) [E]
Sent: Sat, 1 Feb 2020 18:43:31 +0000
To: Kristian G. Andersen
Subject: RE: FW: Science: Mining coronavirus genomes for clues to the outbreak's origins

Thanks, Kristian. Talk soon on the call.

From: Kristian G. Andersen [redacted (b) (6)>
Sent: Friday, January 31, 2020 10:32 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted (b) (6)
Cc: Jeremy Farrar [redacted (b) (6)>
Subject: Re: FW: Science: Mining coronavirus genomes for clues to the outbreak's origins

Hi Tony,

Thanks for sharing. Yes, I saw this earlier today and both Eddie and myself are actually quoted in it. It's a great article, but the problem is that our phylogenetic analyses aren't able to answer whether the sequences are unusual at individual residues, except if they are completely off. On a phylogenetic tree the virus looks totally normal and the close clustering with bats suggest that bats serve as the reservoir. The unusual features of the virus make up a really small part of the genome (<0.1%) so one has to look really closely at all the sequences to see that some of the features (potentially) look engineered.

We have a good team lined up to look very critically at this, so we should know much more at the end of the weekend. I should mention that after discussions earlier today, Eddie, Bob, Mike, and myself all find the genome inconsistent with expectations from evolutionary theory. But we have to look at this much more closely and there are still further analyses to be done, so those opinions could still change.

Best,
Kristian

On Fri, Jan 31, 2020 at 18:47 Fauci, Anthony (NIH/NIAID) [E] [redacted (b) (6)> wrote:

> Jeremy/Kristian:
> This just came out today. You may have seen it. If not, it is of interest to the current discussion.
> Best,
> Tony

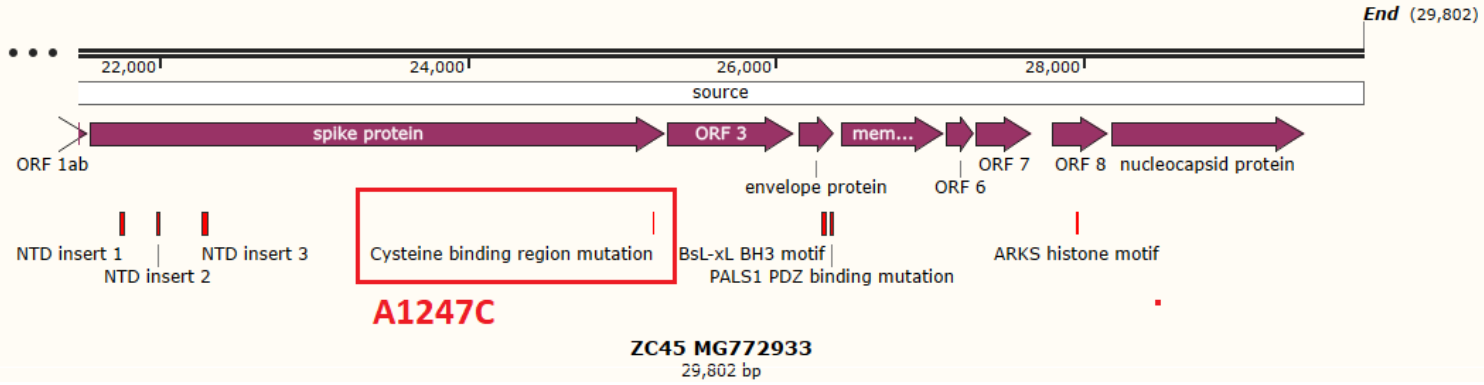
says. 'It happens in nature.' Kristian cautioned that just because it happened in nature did not rule out unnatural origins, especially as closely related coronaviruses lacked some of the same structural features. Ron, meanwhile, worried that focusing on what seemed like an outlandish question would end up distracting busy researchers. We needed to solicit further opinions, especially as Eddie and Kristian were still nursing concerns. 'At that point,' confesses Eddie, 'I was about 80 per cent sure this thing had come out of a lab.' Kristian was about 60 to 70 per cent convinced in the same direction. Andrew and Bob were not far behind. I, too, was going to have to be persuaded that things were not as sinister as they seemed. Patrick Vallance informed the intelligence agencies of the suspicions; Eddie did the same in Australia. Tony

	Published by	Envelope (E) Protein	S2 "Cysteine rich region"
SARS-COV-2		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
Known Before SARS-COV-2 (Jan 2020)			
ZC45	PLA Nanjing Command	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
ZC21	PLA Nanjing Command	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGFCCKFDEDDSEPVLKGVKLHYT
SARS (Urbani)		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSWYVYSRVKNLNSSRVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018A		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rp/Shaanxi2011		MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSVGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4247		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018B		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
As6526		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4237		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Longquan-140		MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4081		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
BetaCoV/GX2013		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
HKU3-1		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2013		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs806/2006		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Cp/Yunnan2011		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs3367		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
WIV1		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018D		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4255		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs_672/2006		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
WIV16		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
RsSHC014		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
SARS (Civet)		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs9401		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDPEPVLKGVKLHYT
Rs4084		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs7327		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Anlong-103		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
SC2018		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTIYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018C		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
"Discovered" After SARS-COV-2			
RaTG13 (ca. Jan 20, 2020)	Wuhan Institute of Virology	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
Pangolin Covs (March 26, 2020)	PLA Academy of Military Medical Scoences	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV	LCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

We recently learned Eddie Holmes was also involved in the discovery of RaTG13 (or 4991 as it was known). He forgot to tell anyone about this.

Finding the origin isn't just about assigning blame. The failure to investigate potentially engineered mutations may have an ongoing high cost in human health and lives. Let's look at the mutations and what was known about the regions they occur, from earlier SARS research.

First, a single amino acid mutation in a conserved part of S2. All 3 nucleotides differ. This is highly unlikely to happen in nature. This region in SARS was studied by Mike Farzan, Kristian Andersen's colleague at Scripps. Perhaps this is why he initially suspected engineering?



Richard H. Ebright
@R_H_Ebright

"Farrar noted, for example, that Mike Farzan (dubbed the 'discoverer of SARS receptor' and a professor of immunology at Scripps Research) found a key aspect of the virus "highly unlikely" to have developed outside a lab."

9:14 AM · Jan 12, 2022 · Twitter Web App

	S2 "Cysteine rich region"
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Known Before SARS-COV-2 (Jan 2020)	
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As6526	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Rs4237	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Longquan-140	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
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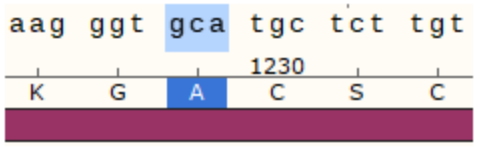
Rs7327	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
Anlong-103	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
SC2018	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
YN2018C	LCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT

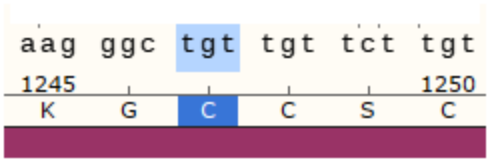
We can deduce from Farzan et al, substituting a Cysteine for Alanine here might enhance fusion between virus and host cells, increasing viral load. Subsequent study of this region happened at China's Fudan University (where Eddie Holmes is a guest Prof).

pubmed.ncbi.nlm.nih.gov/17134730/

SARS like consensus



SARS-COV-2



PubMed.gov

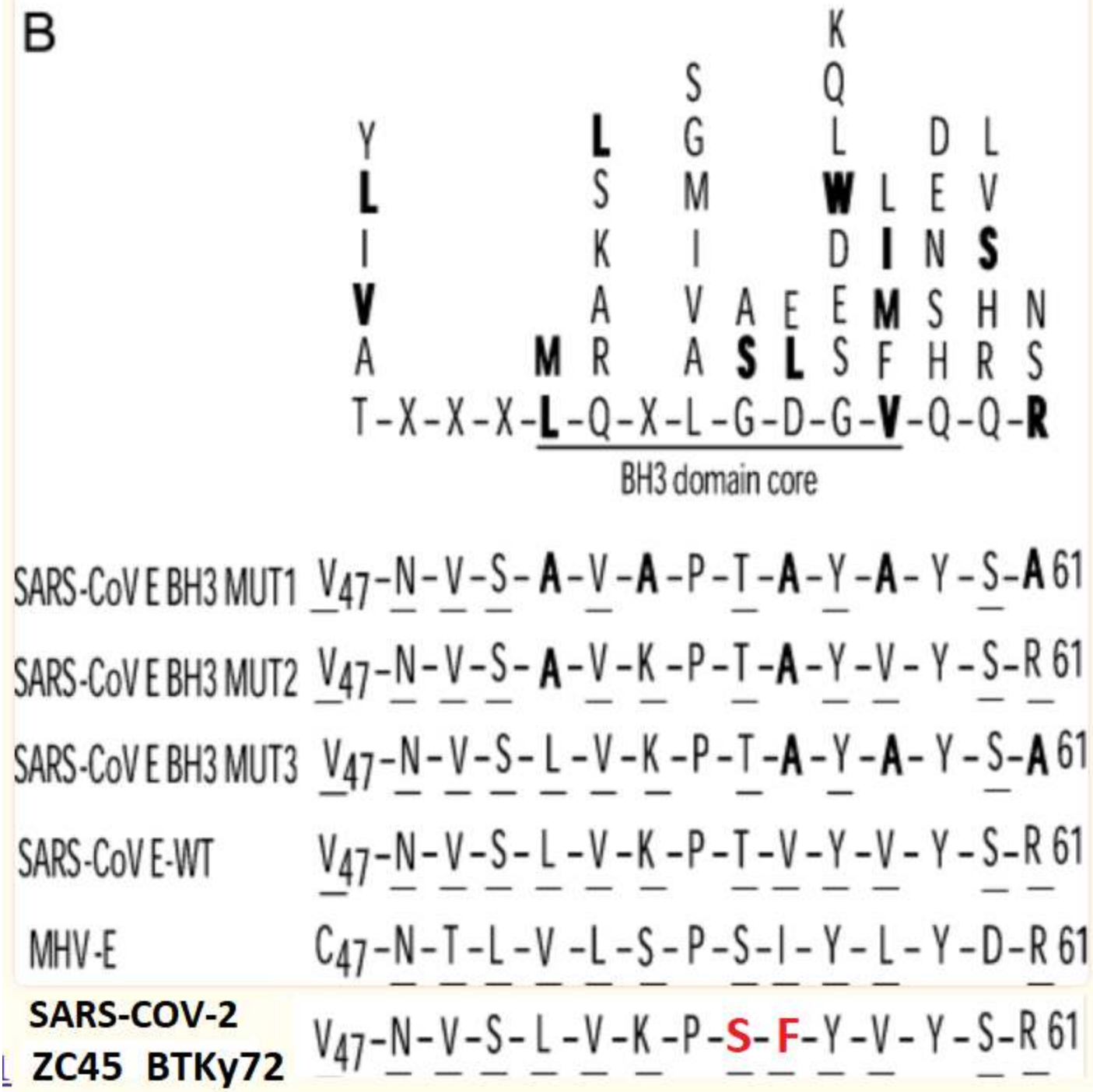
Palmitoylation of the cysteine-rich endodomain of the SARS-coronavirus spike glycoprotein is important for spike-mediated cell fusion - PubMed The SARS-coronavirus (SARS-CoV) is the etiological agent of the severe acute respiratory syndrome (SARS). The SARS-CoV spike (S) glycoprotein mediates membrane fusion events during virus entry and vir...
https://pubmed.ncbi.nlm.nih.gov/17134730/

Next, a region in the Envelope (E) protein that was studied first by scientists at Baylor College. It was shown responsible for massive death of T-Cells (lymphopenia) in SARS-1 patients.

pubmed.ncbi.nlm.nih.gov/16048439/

Abstract

One of the hallmark findings in patients suffering from SARS (severe acute respiratory syndrome) is lymphopenia, which is the result of massive lymphocyte death. SARS-CoV (SARS coronavirus), a novel coronavirus that has been etiologically associated with SARS cases, is homologous with MHV (murine hepatitis coronavirus), and MHV small envelope E protein is capable of inducing apoptosis. We hypothesized that SARS-CoV encodes a small envelope E protein that is homologous with MHV E protein, thus inducing T-cell apoptosis. To test this hypothesis, a cDNA encoding SARS-CoV E protein was created using whole gene synthesis. Our results showed that SARS-CoV E protein induced apoptosis in the transfected Jurkat T-cells, which was amplified to higher apoptosis rates in the absence of growth factors. However, apoptosis was inhibited by overexpressed antiapoptotic protein Bcl-xL. Moreover, we found that SARS-CoV E protein interacted with Bcl-xL in vitro and endogenous Bcl-xL in vivo and that Bcl-xL interaction with SARS-CoV E protein was mediated by BH3 (Bcl-2 homology domain 3) of Bcl-xL. Finally, we identified a novel BH3-like region located in the C-terminal cytosolic domain of SARS-CoV E protein, which mediates its binding to Bcl-xL. These results demonstrate, for the first time, a novel molecular mechanism of T-cell apoptosis that contributes to the SARS-CoV-induced lymphopenia observed in most SARS patients.


B
T-X-X-X-L-Q-X-L-G-D-G-V-Q-Q-R
BH3 domain core
SARS-CoV E BH3 MUT1 V47-N-V-S-A-V-A-P-T-A-Y-A-Y-S-A 61
SARS-CoV E BH3 MUT2 V47-N-V-S-A-V-K-P-T-A-Y-V-Y-S-R 61
SARS-CoV E BH3 MUT3 V47-N-V-S-L-V-K-P-T-A-Y-A-Y-S-A 61
SARS-CoV E-WT V47-N-V-S-L-V-K-P-T-V-Y-V-Y-S-R 61
MHV-E C47-N-T-L-V-L-S-P-S-I-Y-L-Y-D-R 61
SARS-COV-2 V47-N-V-S-L-V-K-P-S-F-Y-V-Y-S-R 61
ZC45 BTKy72

Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors - PubMed One of the hallmark findings in patients suffering from SARS (severe acute respiratory syndrome) is lymphopenia, which is the result of massive lymphocyte death. SARS-CoV (SARS coronavirus), a novel c... https://pubmed.ncbi.nlm.nih.gov/16048439/

But this mutation is not quite unique. It is seen once before in a distantly related virus from Kenya, BtKY72, found by US CDC...and Eddie Holmes. The

virus was found in 2007-09 but only made public in 2019.

pubmed.ncbi.nlm.nih.gov/28077633/

Surveillance of Bat Coronaviruses in Kenya Identifies Relatives of Human Coronaviruses NL63 and 229E and Their Recombination History

Ying Tao [1], Mang Shi [2], Christina Chommanard [1], Krista Queen [1], Jing Zhang [1], Wanda Markotter [3], Ivan V Kuzmin [4], Edward C Holmes [2], Suxiang Tong [5]

Affiliations – collapse

Affiliations

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2 Marie Bashir Institute for Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Life and Environmental Sciences and Sydney Medical School, The University of Sydney, Sydney, Australia.
3 Centre for Viral Zoonoses, Department of Medical Virology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.
4 Division of High Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
5 Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA sot1@cdc.gov.

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RsSHC014		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV
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YN2018C		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
BtKY72 (Kenya)	US CDC (+Eddie Holmes)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYIYSRVKNLNSSQGIPDLLV
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Pangolin Covs (March 26, 2020)	PLA Academy of Military Medical Scoences (+Eddie Homes)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
RmYN02 (June 8, 2020)	Shandong First Medical University (+Eddie Holmes)	

Surveillance of Bat Coronaviruses in Kenya Identifies Relatives of Human Coronaviruses NL63 and 229E and Their Recombination History - PubMed
Bats harbor a large diversity of coronaviruses (CoVs), several of which are related to zoonotic pathogens that cause severe disease in humans. Our screening of bat samples collected in Kenya from 2007...
https://pubmed.ncbi.nlm.nih.gov/28077633/

A unique mutation at the CTD end of E. This region was first studied by Malik

Peiris et al HKU Pasteur. It binds host protein PALS1, speculatively enabling destruction of lung epithelium.

The SARS-COV-2 mutation is thought to strengthen the binding.

pubmed.ncbi.nlm.nih.gov/20861307/

Intercellular tight junctions define epithelial apicobasal polarity and form a physical fence which protects underlying tissues from pathogen invasions. PALS1, a tight junction-associated protein, is a member of the CRUMBS3-PALS1-PATJ polarity complex, which is crucial for the establishment and maintenance of epithelial polarity in mammals. Here we report that the carboxy-terminal domain of the SARS-CoV E small envelope protein (E) binds to human PALS1. Using coimmunoprecipitation and pull-down assays, we show that E interacts with PALS1 in mammalian cells and further demonstrate that the last four carboxy-terminal amino acids of E form a novel PDZ-binding motif that binds to PALS1 PDZ domain. PALS1 redistributes to the ERGIC/Golgi region, where E accumulates, in SARS-CoV–infected Vero E6 cells. Ectopic expression of E in MDCKII epithelial cells significantly alters cyst morphogenesis and, furthermore, delays formation of tight junctions, affects polarity, and modifies the subcellular distribution of PALS1, in a PDZ-binding motif-dependent manner. We speculate that hijacking of PALS1 by SARS-CoV E plays a determinant role in the disruption of the lung epithelium in SARS patients.

	Published by	Envelope (E) Protein
SARS-COV-2		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
Known Before SARS-COV-2 (Jan 2020)		
ZC45	PLA Nanjing Command	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
ZC21	PLA Nanjing Command	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
SARS (Urbani)		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
YN2018A		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rp/Shaanxi2011		MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSVGVPDLLV
Rs4247		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV
YN2018B		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
As6526		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs4237		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Longquan-140		MYSFVSEETGTLIVNSVLLFFAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs4081		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
BetaCoV/GX2013		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
HKU3-1		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
YN2013		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs806/2006		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Cp/Yunnan2011		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs3367		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
WIV1		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
YN2018D		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs4255		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs_672/2006		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
WIV16		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
RsSHC014		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV
SARS (Civet)		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Rs9401		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVLDLLV
Rs4084		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSQGVPDLLV
Rs7327		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
Anlong-103		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
SC2018		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTIYVYSRVKNLNSSEGVPDLLV
YN2018C		MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
"Discovered" After SARS-COV-2		
RaTG13 (ca. Jan 20, 2020)	Wuhan Institute of Virology (+Eddie Holmes)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
Pangolin Covs (March 26, 2020)	PLA Academy of Military Medical Scoences (+Eddie Homes)	MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNSS-RVPDLLV
RmYN02 (June 8, 2020)	Shandong First Medical University (+Eddie Holmes)	

The Envelope (E) protein of SARS-CoV-2 is the most enigmatic protein among the four structural ones. Most of its current knowledge is based on the direct comparison to the SARS E protein, initially mistakenly undervalued and subsequently proved to be a key factor in the ER-Golgi localization and in tight junction disruption. We compared the genomic sequences of E protein of SARS-CoV-2, SARS-CoV and the closely related genomes of bats and pangolins obtained from the GISAID and GenBank databases. When compared to the known SARS E protein, we observed a significant difference in amino acid sequence in the C-terminal end of SARS-CoV-2 E protein. Subsequently, in silico modelling analyses of E proteins conformation and docking provide evidences of a strengthened binding of SARS-CoV-2 E protein with the tight junction-associated PALS1 protein. Based on our computational evidences and on data related to SARS-CoV, we believe that SARS-CoV-2 E protein interferes more stably with PALS1 leading to an enhanced epithelial barrier disruption, amplifying the inflammatory processes, and promoting tissue remodelling. These findings raise a warning on the underestimated role of the E protein in the pathogenic mechanism and open the route to detailed experimental investigations.

The SARS coronavirus E protein interacts with PALS1 and alters tight junction formation and epithelial morphogenesis - PubMed Intercellular tight junctions define epithelial apicobasal polarity and form a physical fence which protects underlying tissues from pathogen invasions. PALS1, a tight junction-associated protein, is ... https://pubmed.ncbi.nlm.nih.gov/20861307/

HKU Microbiology department also houses the PRC State Key Lab for Emerging Infectious Disease that contributed to the Pangolin Cov

sequences.

Chinese defector @drLiMenYang1, then at HKU, discusses her work there, her supervisors and Malik Peiris:

theweek.in/theweek/cover/...

Epub 2020 Mar 26.

Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins

Tommy Tsan-Yuk Lam [# 1 2], Na Jia [# 3], Ya-Wei Zhang [# 3], Marcus Ho-Hin Shum [# 2], Jia-Fu Jiang [# 3], Hua-Chen Zhu [1 2], Yi-Gang Tong [# 4], Yong-Xia Shi [5], Xue-Bing Ni [2], Yun-Shi Liao [2], Wen-Juan Li [4], Bao-Gui Jiang [3], Wei Wei [6], Ting-Ting Yuan [3], Kui Zheng [5], Xiao-Ming Cui [3], Jie Li [3], Guang-Qian Pei [3], Xin Qiang [3], William Yiu-Man Cheung [2], Lian-Feng Li [7], Fang-Fang Sun [5], Si Qin [3], Ji-Cheng Huang [5], Gabriel M Leung [2], Edward C Holmes [8], Yan-Ling Hu [9 10], Yi Guan [11 12], Wu-Chun Cao [13]

Affiliations – collapse

What's he doing here?

PLA Colonel
Acadamy of Military Medical Sciences

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# Contributed equally.

HKU Microbiology

Academy of Military Medical Sciences (PLA)

Made in China Covid-19 virus was developed in Chinese lab, WHO suppressed it: Chinese virologist https://www.theweek.in/theweek/cover/2020/10/01/made-in-china.html

There's also an ongoing collaboration between HKU and Zhejiang University. ZU is home to one of the key authors of the ZC45 paper. It's also home to the founder of the 973 program, China's military program to harvest knowledge from civilian and overseas institutions.

Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats

Dan Hu [1] [2], Changqiang Zhu [2], Lele Ai [2], Ting He [2], Yi Wang [3], Fuqiang Ye [2], Lu Yang [2], Chenxi Ding [2], Xuhui Zhu [2], Ruicheng Lv [2], Jin Zhu [2], Bachar Hassan [4], Youjun Feng [5], Weilong Tan [6], Changjun Wang [7] [8]

Affiliations – collapse

PLA Colonels

Previously 973 program scholar in US. Colleague of Shibo Jiang (New York Blood Center, Fudan University)

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4 Stony Brook University, Stony Brook, 11794, USA.
5 Department of Pathogen Biology & Microbiology and Department of General Intensive Care Unit of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310058, China. fengyj@zju.edu.cn.
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8 Department of Epidemiology, Research Institute for Medicine of Nanjing Command, Nanjing, 210002, China. science2008@hotmail.com.

ZC45/ZXC21 discovery paper author affiliations

CHINA DEFENCE UNIVERSITIES TRACKER

ASPI AUSTRALIAN STRATEGIC POLICY INSTITUTE | INTERNATIONAL CYBER POLICY CENTRE

Zhejiang University

浙江大学

Zhejiang University (ZJU) is designated high risk for its moderately high number of defence laboratories, relationship with defence industry, and links to economic and cyber espionage.

HIGH
RISK CATEGORY

SECRET
SECURITY CREDENTIALS

3 MAJOR DEFENCE LABORATORIES

1+ DESIGNATED DEFENCE RESEARCH AREAS

ESPIONAGE OR MISCONDUCT

ZJU is subordinate to the Ministry of Education and jointly constructed with defence industry agency SASTIND. This arrangement with SASTIND began in 2016 and is designed to deepend the university's involvement in defence research. [1] The university holds secret-level security credentials, allowing it to work on classified military projects. [2]

The university's total research funding amounts to RMB4.56 billion (AUD940 million) in 2018. [3] It has at least three defence laboratories, with one source claiming that the university had ten key national laboratories (国家重点实验室) as of 2015. [4] These laboratories are involved in research on computer simulations, high-performance computing and control science. The university also carries out cyber security research and receives funding for this work from the MSS, China's civilian intelligence agency. [5]

ZJU cooperates extensively with international universities and companies, with upwards of 40 international joint S&T research labs. [6] The College of Electrical Engineering has joint labs with U.S. companies in key industries, such as Rockwell Automation in the field of information technology, and the National Semiconductor Corporation. Additionally, the university has a joint research lab with U.S company Microsoft. [7]

Aliases

浙江大学

ZJU

< Back

HKU furthers collaborative ties with Mainland research institutes

10 Mar 2013

The University of Hong Kong (HKU) has been engaged in a number of projects for further collaboration with its partner research institutions in the Mainland.

On February 1, 2013, a draft agreement on "HKU-Zheda-Tsinghua collaborative research and innovation lab on infectious disease treatment" was signed with Zhejiang University and Tsinghua University Beijing to cooperate together with the Chinese Center for Disease Control and Prevention, and other Mainland research institutes and academics in areas of knowledge and talent exchanges, postgraduate students training and sharing of research resources.

On February 6, an opening Ceremony was held for the Hong Kong-Guangdong Joint Laboratory on Stem Cell and Regenerative Medicine, which is established at the HKU Li Ka Shing Faculty of Medicine and co-managed by Guangzhou Institutes of Biomedicine and Health (GIBH) under the Chinese Academy of Sciences and HKU. With an aim to better human health, the laboratory will facilitate knowledge exchange and will promote collaborations between HKU and GIBH researchers, as well as will further advance the clinical research on stem cell and regenerative medicine.

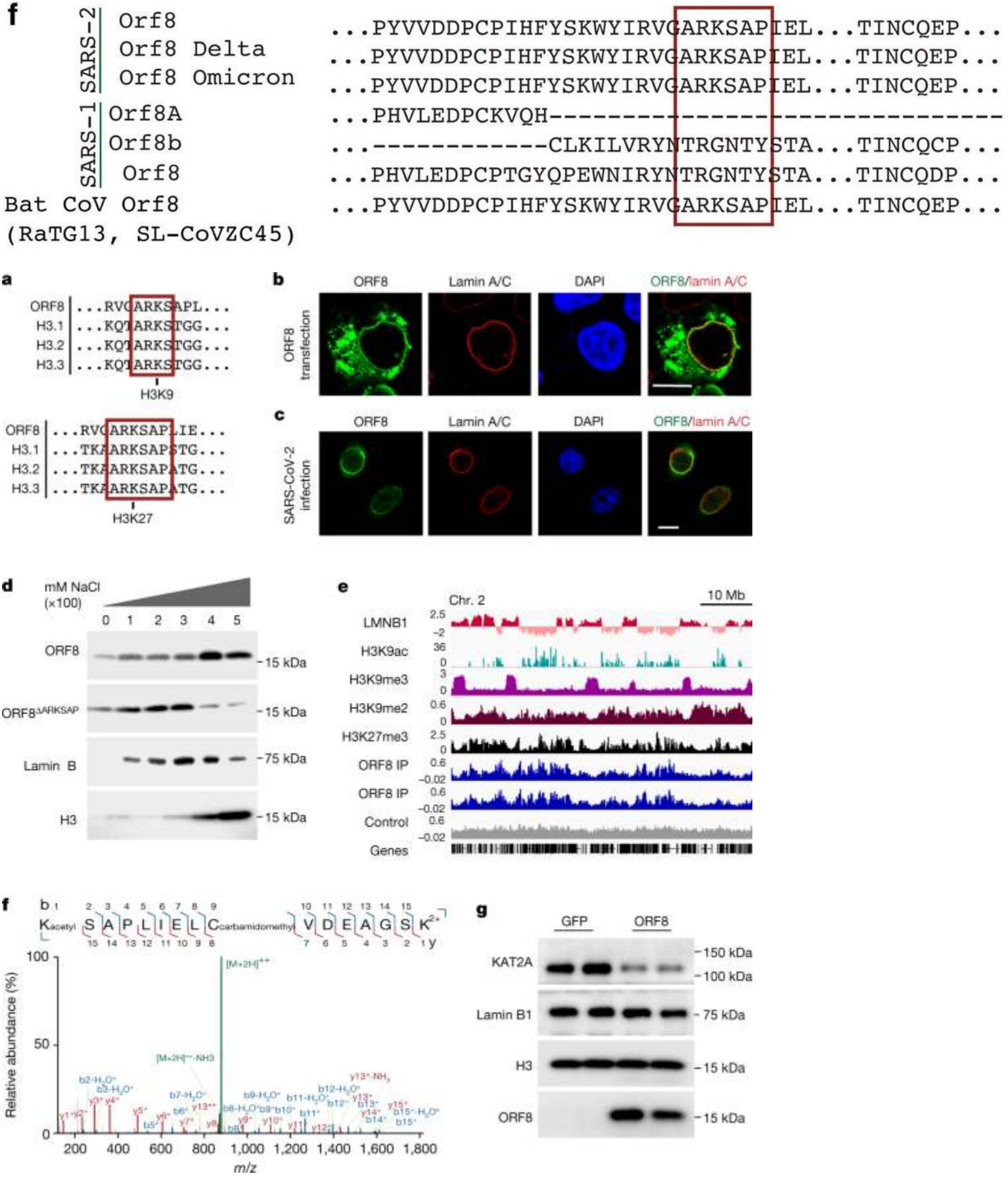
On February 16, a Foundation Stone-Laying Ceremony of the University of Hong Kong Zhejiang Institute of Research and Innovation (HKU-ZIRI) cum Tree Planting was held at Qingshanhu Science and Technology City in Lin'an of Zhejiang. HKU Vice-Chancellor Professor Lap-Chee Tsui, Pro-Vice-Chancellor Professor Paul Tam, Associate Vice-President Professor Paul Cheung, Dean of Engineering Professor Norman Tien attended the various activities, and had Secretary of CPC Hangzhou Municipal Committee Mr Huang Kunming joined the Tree Planting.

Professor Tsui officiated at the ceremony and said: "As the extension of the research capabilities of the University to the Chinese Mainland, HKU-ZIRI is supposed to carry forward the university's vision to contribute to the advancement of society and the development of leaders through a global presence, regional significance and engagement with the rest of China.

A recent discovery - histone mimicry motif ARKS in SARS-COV-2, also appears in ZC45, but not other previously known sarbecovs.

(I've yet to do a comprehensive search on this so tbc)

nature.com/articles/s4158...



SARS-CoV-2 disrupts host epigenetic regulation via histone mimicry - Nature The SARS-CoV-2 protein ORF8 functions as a mimic of histone H3 to disrupt host cell epigenetic regulation. https://www.nature.com/articles/s41586-022-05282-z

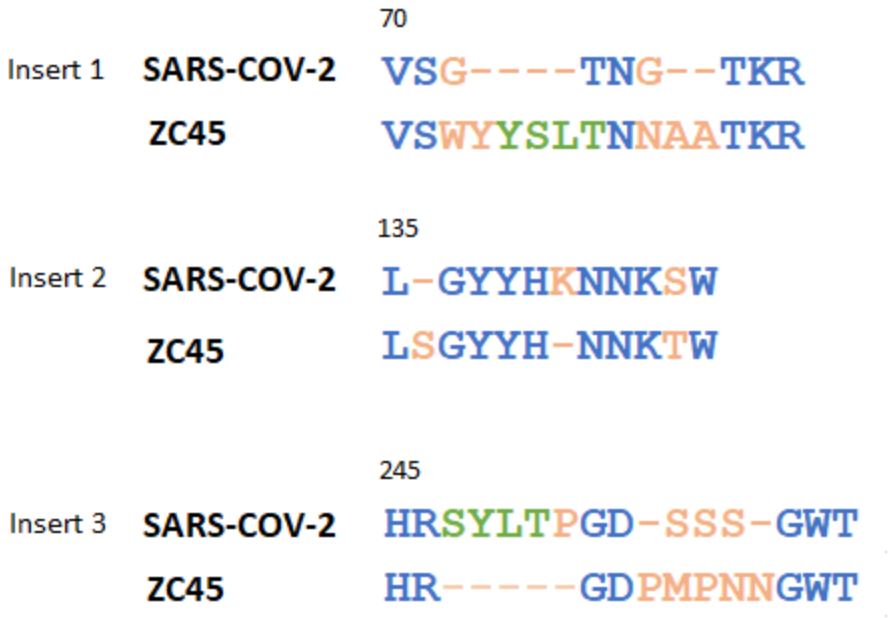
The most interesting shared anomalies are the sites that were initially identified as "HIV inserts" by Pradhan et al. I've covered these in some detail in an earlier thread (please read this first).

Then let's see how they compare in ZC45.

Unroll available on Thread Reader

https://twitter.com/breakfast_dogs/status/1565607550350815232

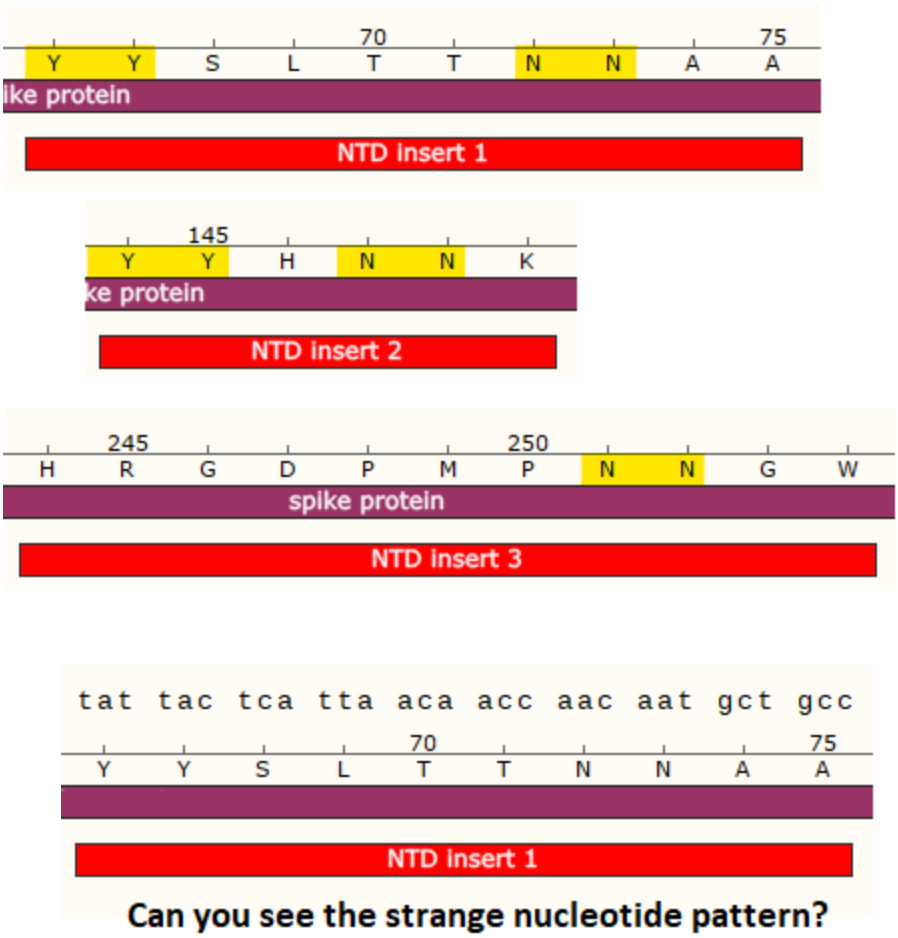
They look a little different to SARS-COV-2 but are much more similar than in other previously known sarbecovs. It's important to note these are in loops attached to the surface of the spike. They interact often with the immune system, so mutations are frequent.



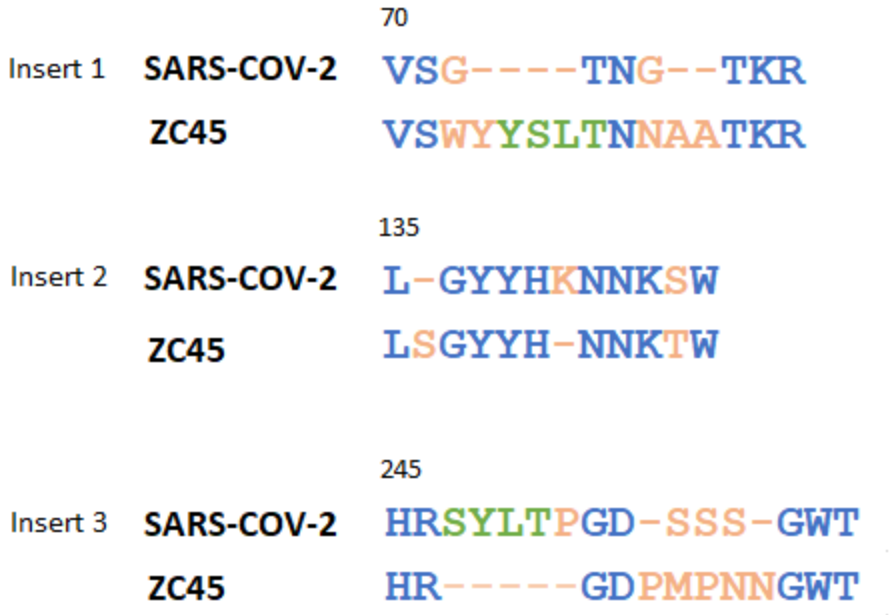
The ZC45 version of these sites also has some strange coincidences and patterns

-each site has an asparagine doublet NN
-2 also have a tyrosine doublet upstream YY
-one has a stretch containing four doublets YYSLTTNNAA with interesting

nucleotide pattern



Looking between the ZC45 and SARS-COV-2 versions of these sites there is something else strange. The residues YSLT seem to have jumped from one site to another 175 amino acids away. Almost as if they've been cut-pasted to a more suitable position.



But what could this all mean? Why all the doublets?

I speculate that ZC45 is an intermediate engineering product. It has some point mutations already, but hasn't yet been human adapted by serial passaging in cell culture, animals, or even in humans.

The doublets are so there's a better chance that one of each will survive passaging without mutating to a different amino acid. This is especially important with asparagine (N) because these provide the basis of N-glycosylation sites. Y is also important.

ncbi.nlm.nih.gov/pmc/articles/P...

Minimalist synthetic antibodies

Go to:

Examination of natural antigen-binding sites has shown that tyrosine is particularly abundant, as it accounts for ~10% of the total composition of the complementarity-determining region (CDR) loops and ~25% of the antigen contacts in functional antibodies [45]. Moreover, analysis of naïve diversity in the third heavy-chain CDR (CDR-H3), which dominates most antigen-binding sites, predicts an even more extreme bias prior to antigen recognition and affinity maturation, as ~40% of the sequence is predicted to be tyrosine and ~30% is predicted to be small amino acids (serine, glycine, alanine and threonine) [46]. While these biases may be the coincidental result of genetic biases in antibody genes, we and others believe that tyrosine, together with small residues that provide conformational freedom and space, is uniquely suited for mediating favorable contacts for antigen recognition [22, 45-47]. Studies with minimalist synthetic antibodies have proven this hypothesis and have provided a path towards designed antibodies with functions beyond those of natural antibodies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2829252/

ZC45 does not have an FCS and its S1/S2 junction looks very similar to old school sarbecovs with just one unique mutation. Newly "discovered" sequences are different and diverse, though none have an FCS. This in itself raises questions for die-hard natural origin proponents.

SARS-COV-2	CASYQTQTNSPRRARSVASQ-SIIAY
Known Before SARS-COV-2 (Jan 2020)	
ZC45	CASYHT--ASIL--RSTS-QKAIVAY
ZC21	CASYHT--ASIL--RSTG-QKAIVAY
SARS (Urbani)	CASYHT--VSLL--RSTS-QKSIVAY
YN2018A	CASYHT--ASTL--RSVG-QKSIVAY
Rp/Shaanxi2011	CASYHT--ASVL--RSTG-QKSIVAY
Rs4247	CASYHT--ASTL--RSVG-QKSIVAY
YN2018B	CASYHT--VSSL--RSTS-QKSIVAY
As6526	CASYHT--ASTL--RSVG-QKSIVAY
Rs4237	CASYHT--ASTL--RSVG-QKSIVAY
Longquan-140	CASYHT--ASVL--RSTG-QKSIVAY
Rs4081	CASYHT--ASTL--RSVG-QKSIVAY
BetaCoV/GX2013	CASYHT--ASVL--RSTG-QKSIVAY
HKU3-1	CASYHT--ASVL--RSTG-QKSIVAY
YN2013	CASYHT--ASTL--RSIG-QKSIVAY
Rs806/2006	CASYHT--ASLL--RSTG-QKSIVAY
Cp/Yunnan2011	CASYHT--ASLL--RNTG-QKSIVAY
Rs3367	CASYHT--VSSL--RSTS-QKSIVAY
WIV1	CASYHT--VSSL--RSTS-QKSIVAY
YN2018D	CASYHT--ASTL--RSVG-QKSIVAY
Rs4255	CASYHT--ASTL--RSVG-QKSIVAY
Rs_672/2006	CASYHT--ASTL--RSVG-QKSIVAY
WIV16	CASYHT--VSSL--RSTS-QKSIVAY
RsSHC014	CASYHT--VSSL--RSTS-QKSIVAY
SARS (Civet)	CASYHT--VSSL--RSTS-QKSIVAY
Rs9401	CASYHT--VSSL--RSTS-QKSIVAY
Rs4084	CASYHT--VSSL--RSTS-QKSIVAY
Rs7327	CASYHT--VSSL--RSTS-QKSIVAY
Anlong-103	CASYHT--ASTL--RSVG-QKSIVAY
SC2018	CASYHT--ASLL--RSTG-QKSIVAY
YN2018C	CASYHT--ASTL--RSTG-QKSIVAY
"Discovered" After SARS-COV-2	
RaTG13 (ca. Jan 20, 2020)	CASYQTQTNS----RSVASQ-SIIAY
Pangolin Covs (March 26, 2020)	CASYHS--MSSF--RSVNQR-SIIAY
RmYN02 (June 8, 2020)	CASY----NSPAA-R-VGTN-SIIAY

If ZC45 is part of a newly discovered natural clade, why does it also have some features of the original SARS-like viruses? It seems to be the missing link between SARS-1 and SARS-COV-2, and deserves far more attention than

it gets.

That should be @DrLiMengYAN1, my mistake!