New data on COVID-19 Origins

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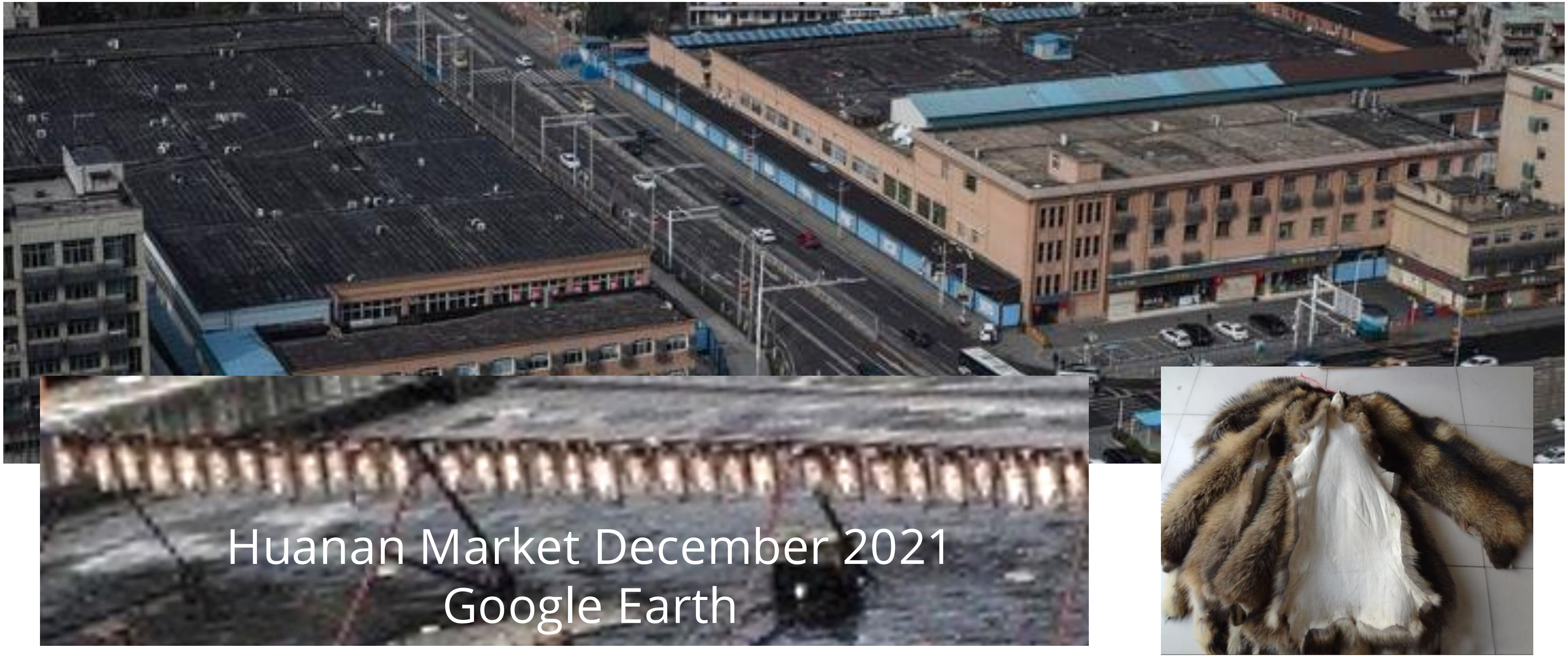
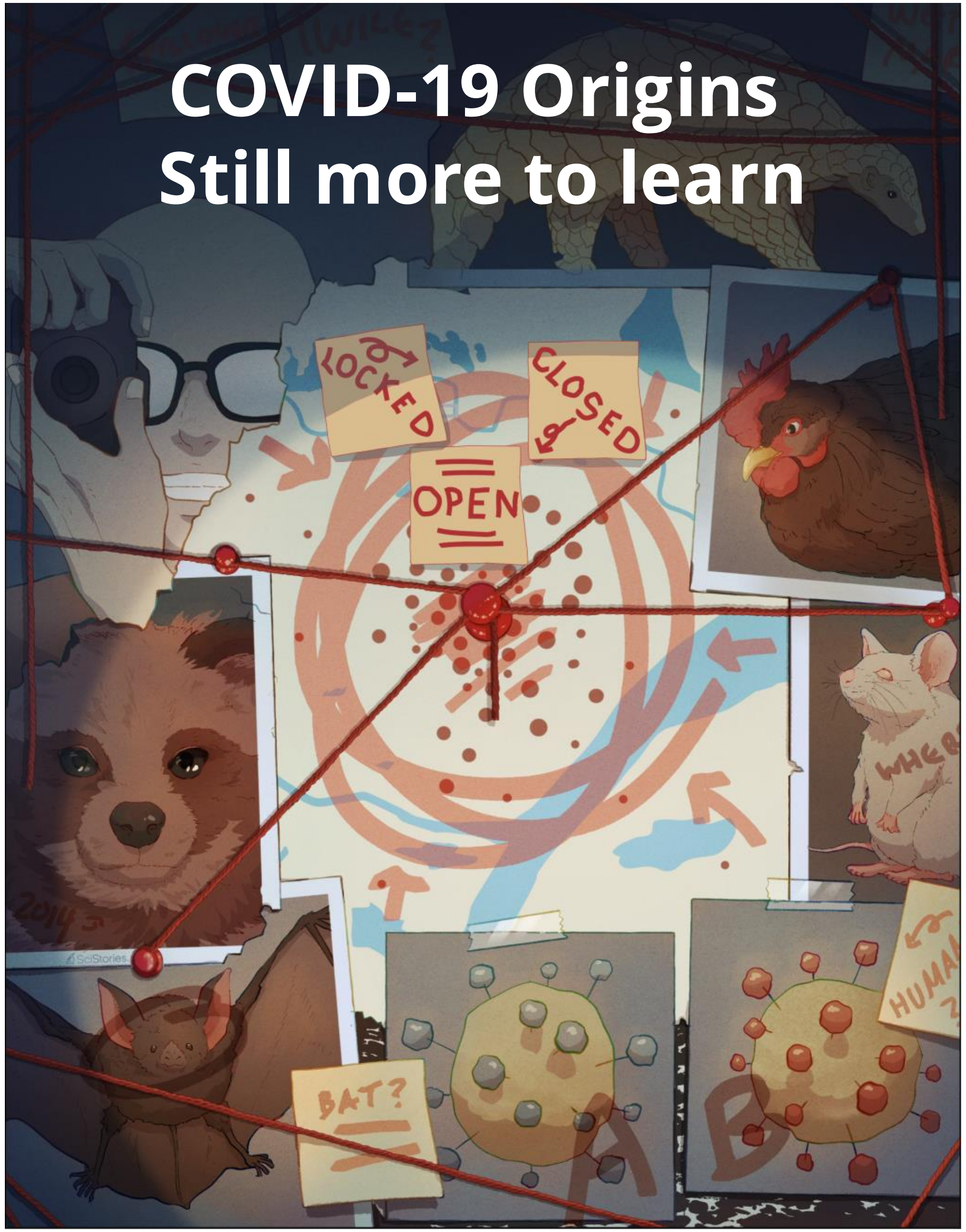
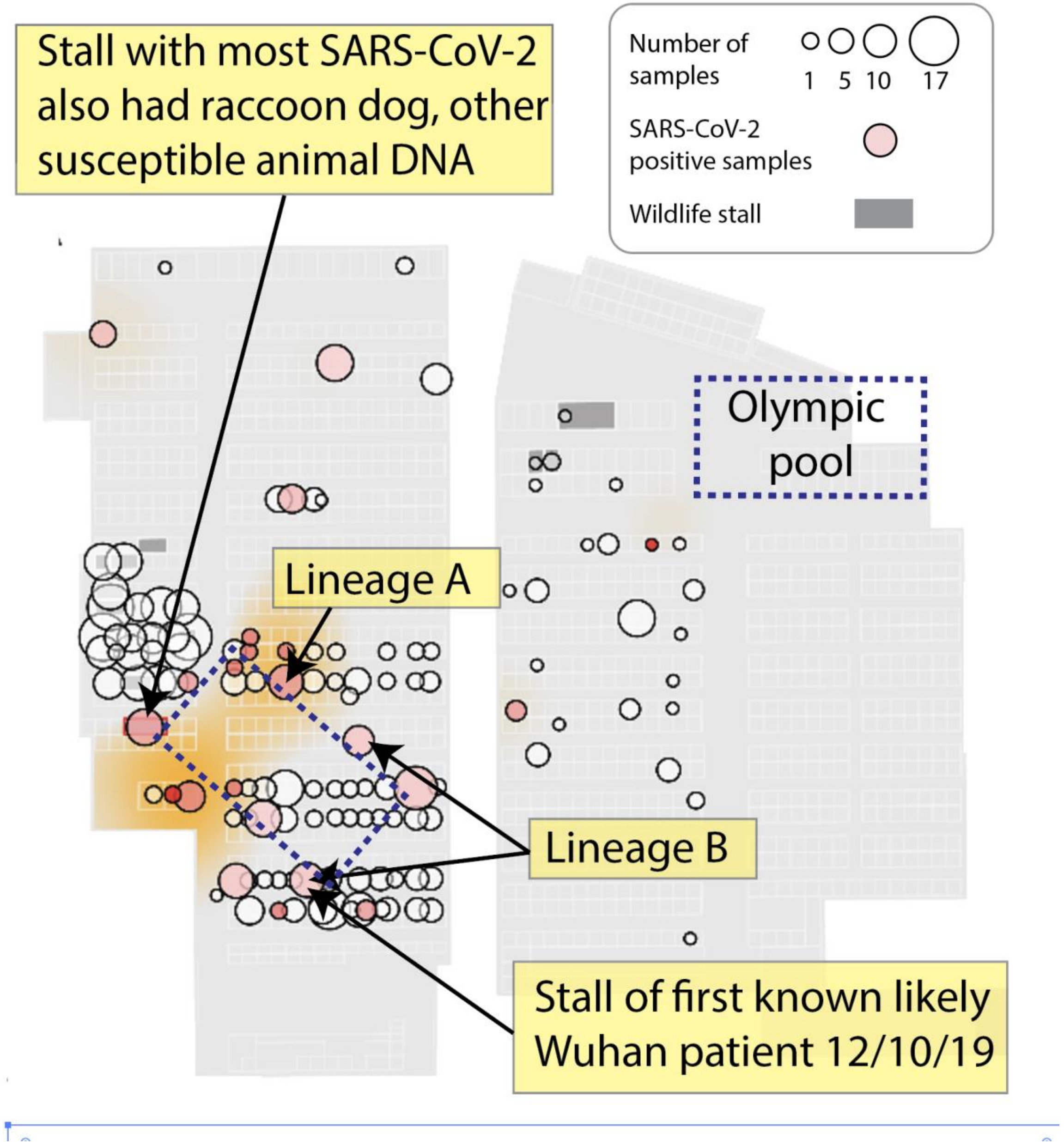
The Huanan Market in Wuhan was the early epicenter of the COVID-19 pandemic



Huanan Market December 2021
Google Earth

COVID-19 Origins
Still more to learn





Stall with most SARS-CoV-2 also had raccoon dog, other susceptible animal DNA

Lineage A

Lineage B

Stall of first known likely Wuhan patient 12/10/19

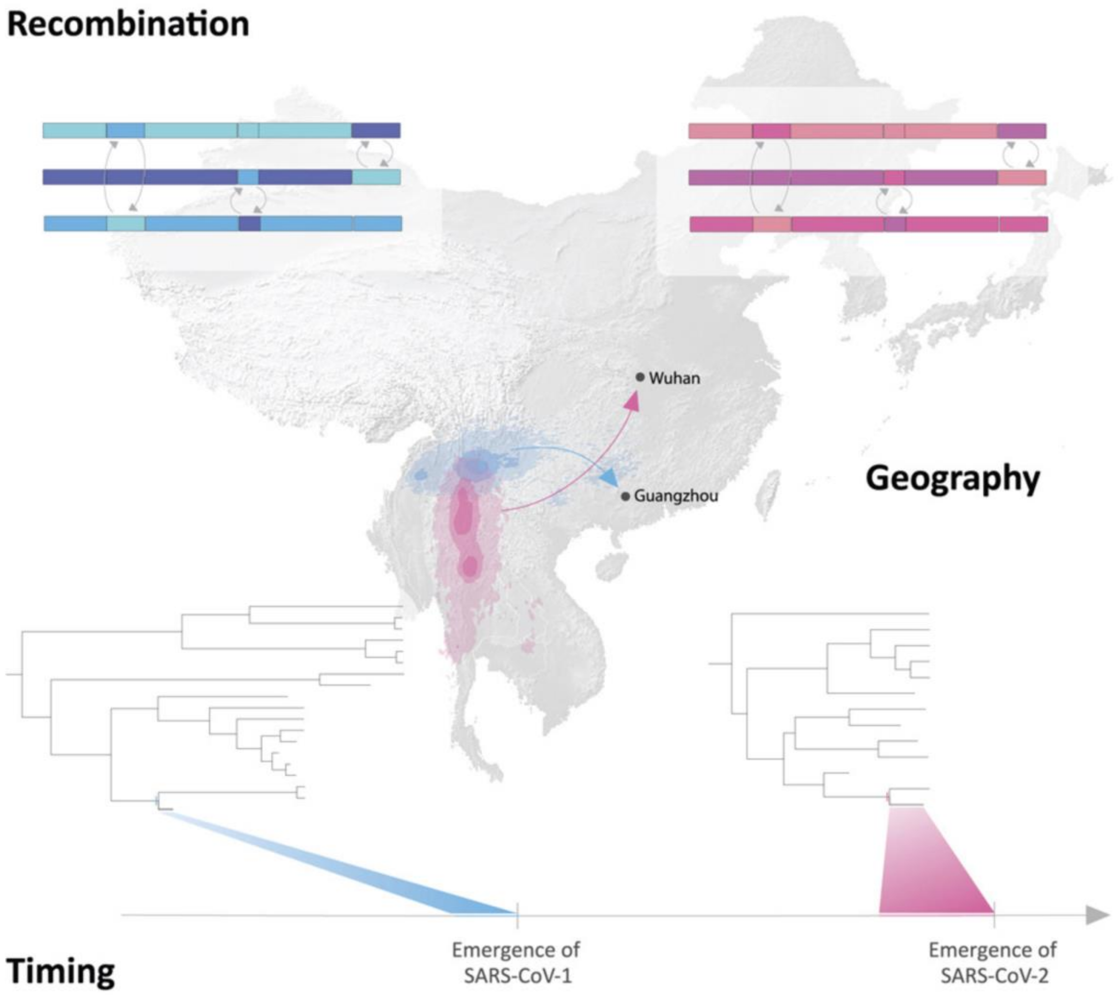
Crits-Christoph et al. Cell. 2024 Sep 19;187(19):5468-5482.

The sarbecoviruses most closely related to SARS-CoV-2 have been detected in bats from the karst terrain common to China, Laos and Vietnam.

Three bat viruses genetically more similar to SARS-CoV-2 than RaTG13, which was previously thought to be the closest relative.

By Jonathan Corum | Sources: Spyros Lytras et al., Science; Sarah Temman et al., Research Square

The bat progenitor of SARS-CoV-2 is highly recombinant and emerged in the decade before COVID-19



- The origin of SARS-CoV-2, as well as SARS-CoV, involve multiple recombination events.

- The closest bat virus ancestors existed less than a decade prior to their emergence in humans.

- The direct ancestors of SARS-CoV-2 and SARS-CoV are unlikely to have reached their respective sites of emergence via dispersal in the bat reservoir alone, supporting interactions with intermediate hosts through wildlife trade playing a role in zoonotic spillover.

Pekar et al., Volume 188, Issue 12, P3167-3183.E18 June 12, 2025

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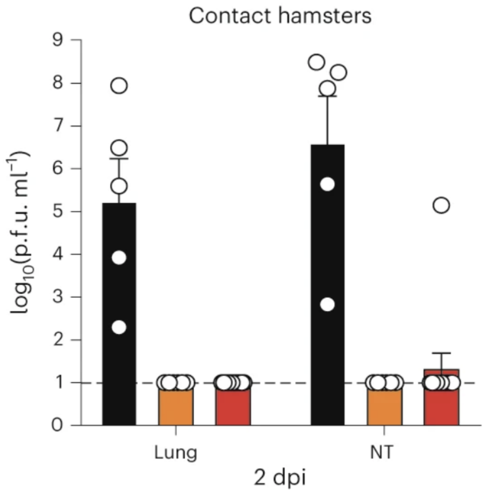
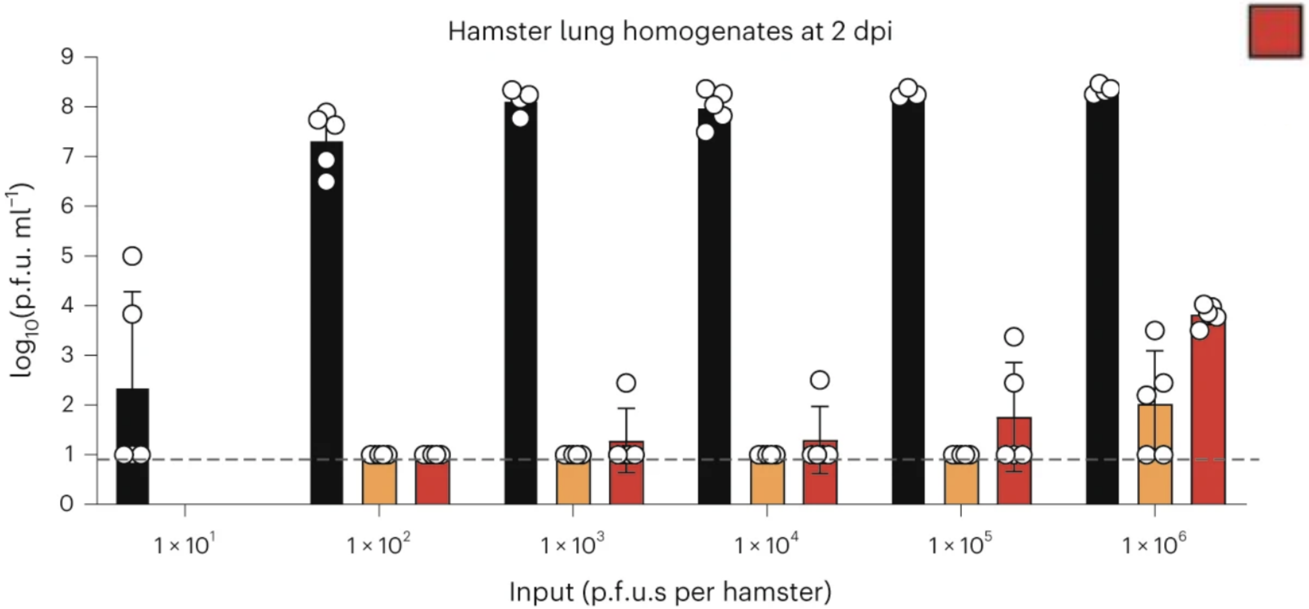
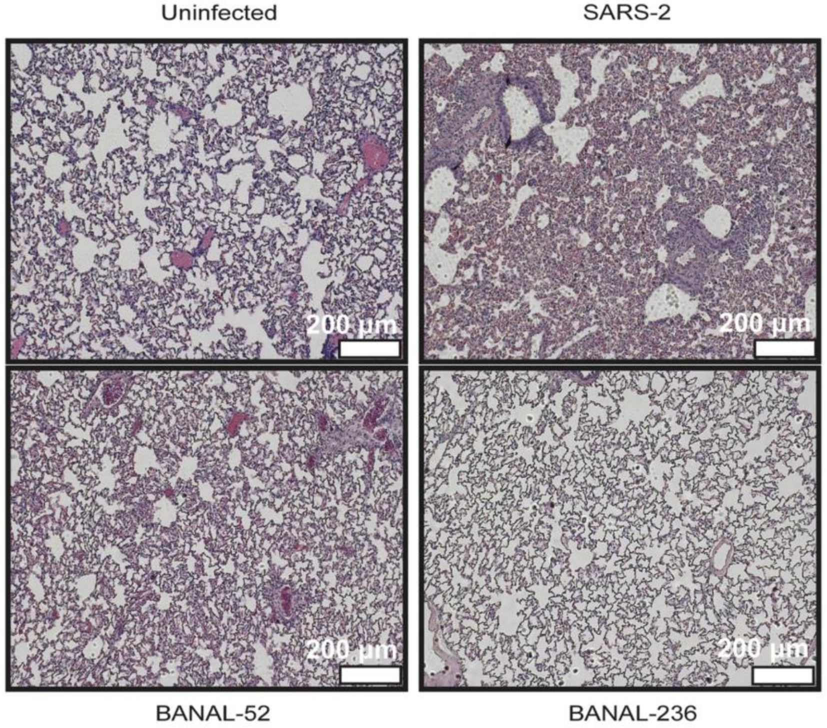
Bat sarbecoviruses don't cause lung pathology and fail to transmit in hamsters

⬛ SARS-2
🟧 BANAL-52
🟥 BANAL-236







Peña-Hernández, M.A., Alfajaro, M.M., Filler, R.B. *et al. Nat Microbiol* **9**, 2038–2050 (2024).
https://doi.org/10.1038/s41564-024-01765-z

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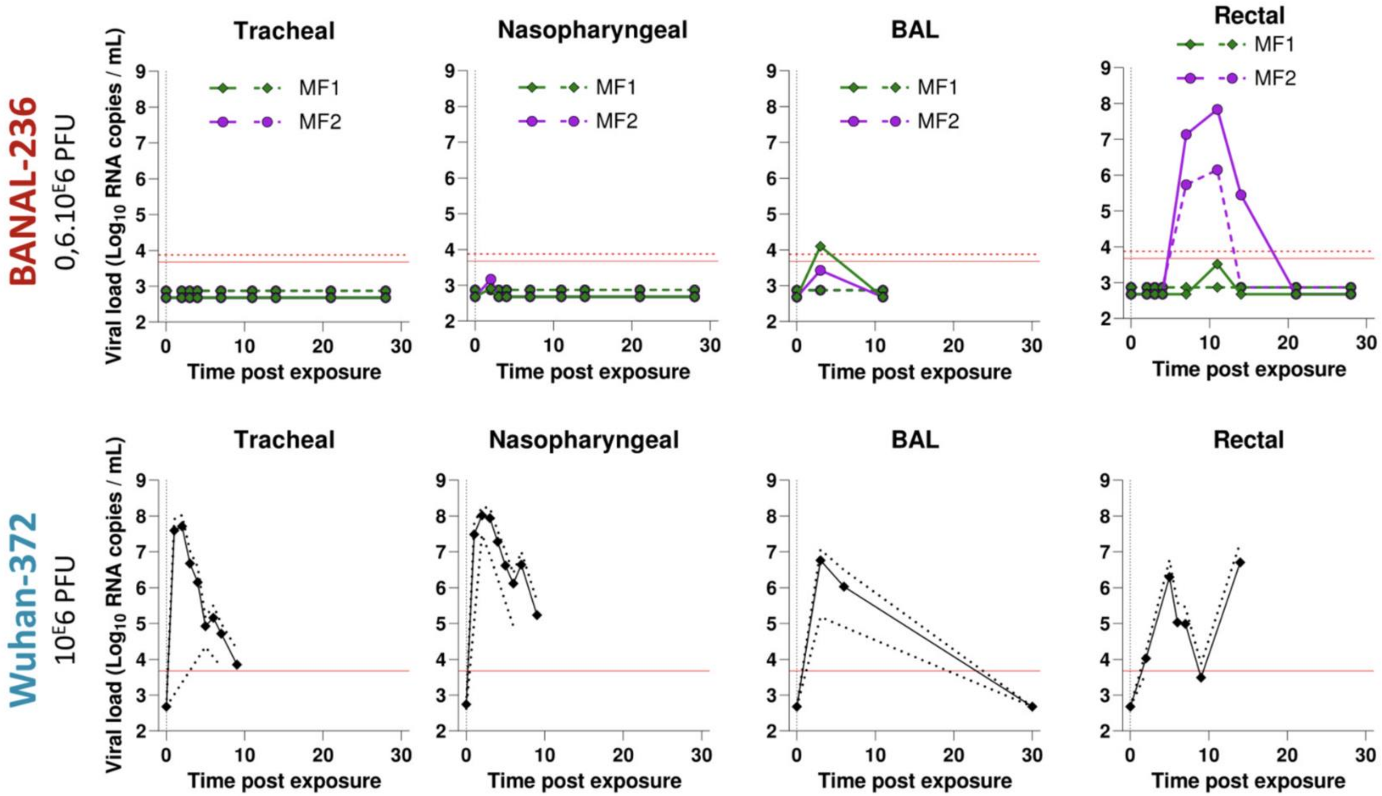
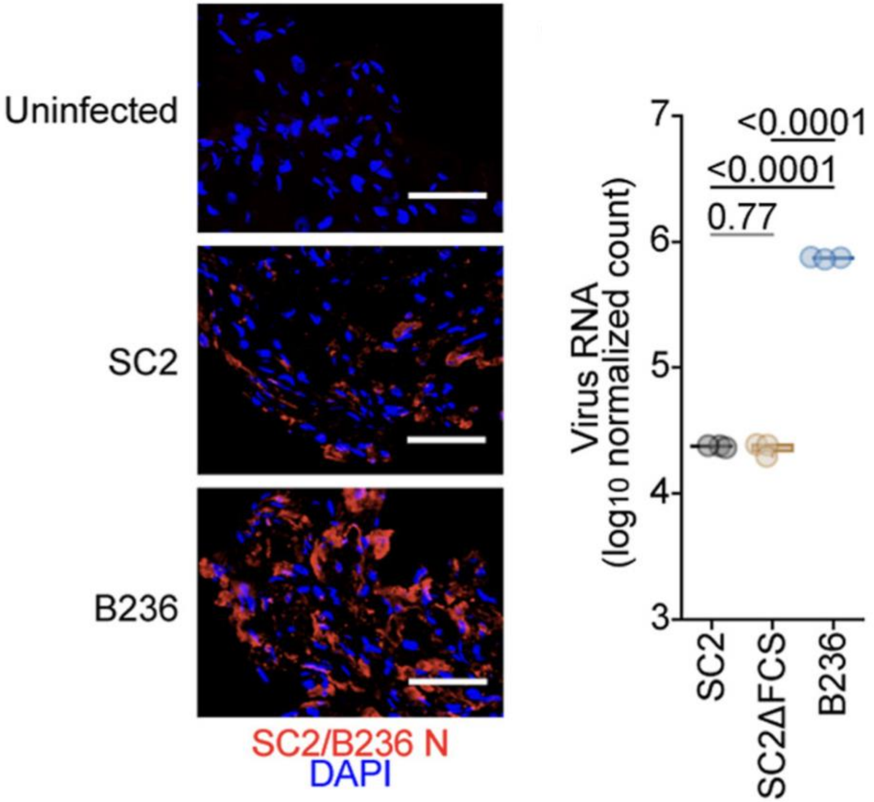
Bat Coronaviruses are GI tropic

Cynomolgus macaques (IN plus IT innoculation)



Temman et al., EMBO rep (2023) 24: e56055

Colon organoids



Fujita et al., eBioMedicine Volume 104, June 2024, 105181

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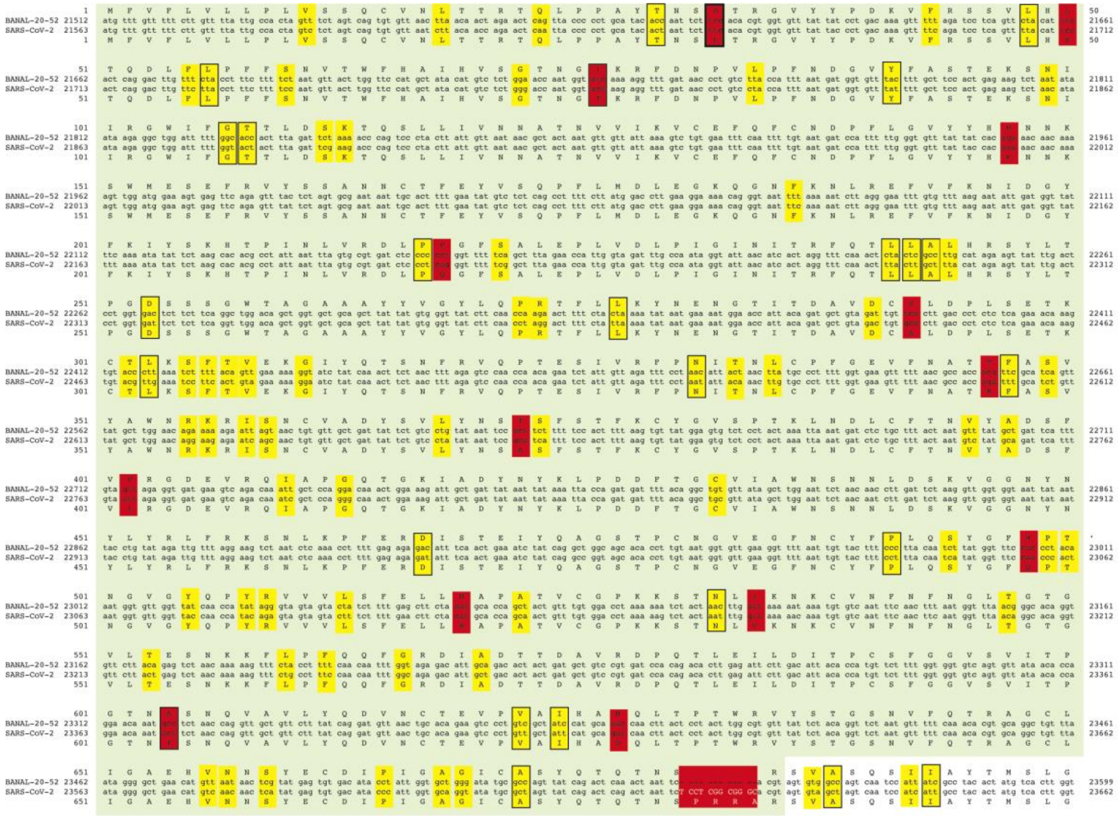
Only 16 amino acids distinguish BANAL-20-52 and SARS-CoV-2 Spikes

S1



S2

- 98.4% amino acid sequence identity and 99.2% chemically similar amino acids.
- S1: 14 amino acid differences and the 4 amino acid FCS insertion. S2: 2 amino acid differences. 🟥
- 138 synonymous changes between the BANAL-20-52 and SARS-CoV-2 Spike genes. 🟨
- 23 of 76 and 23 of 62 synonymous or nonsynonymous changes and in S1 and S2 respectively are C → U. 🟥 🟨

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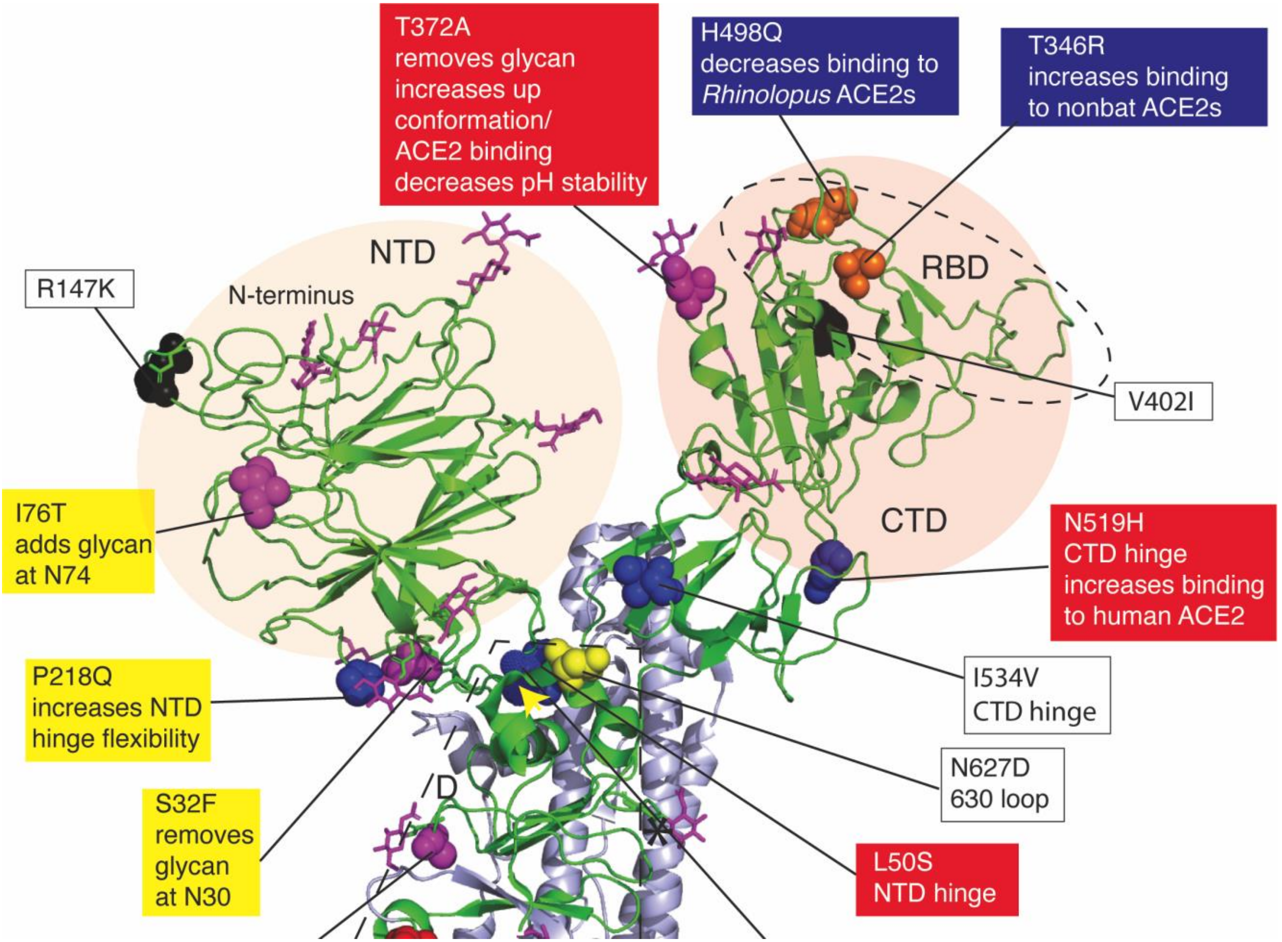
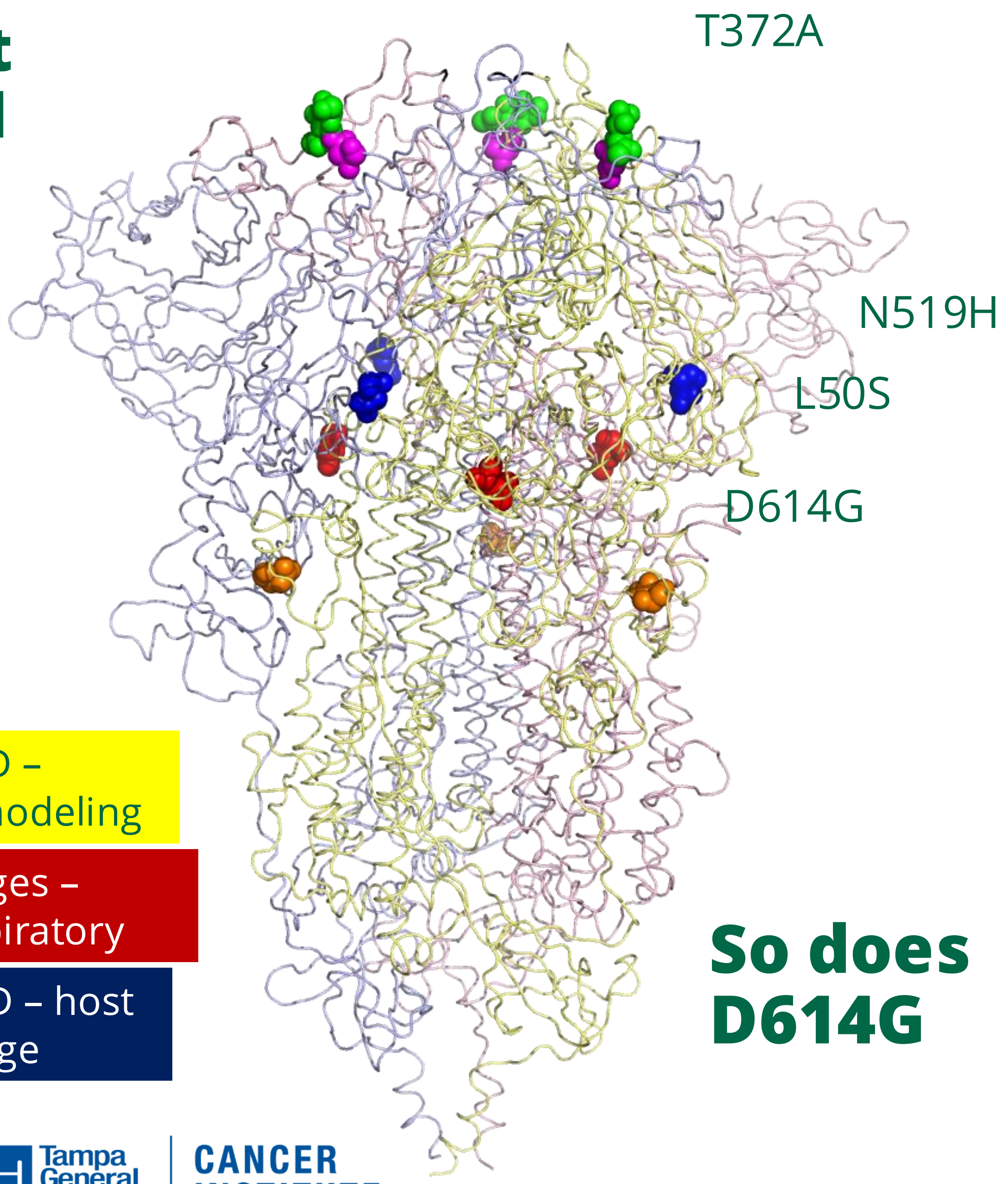
3 of the amino acid differences between BANAL-20-52 and SARS-CoV-2 Spike affect stability, which was critical for GI spread



NTD – remodeling

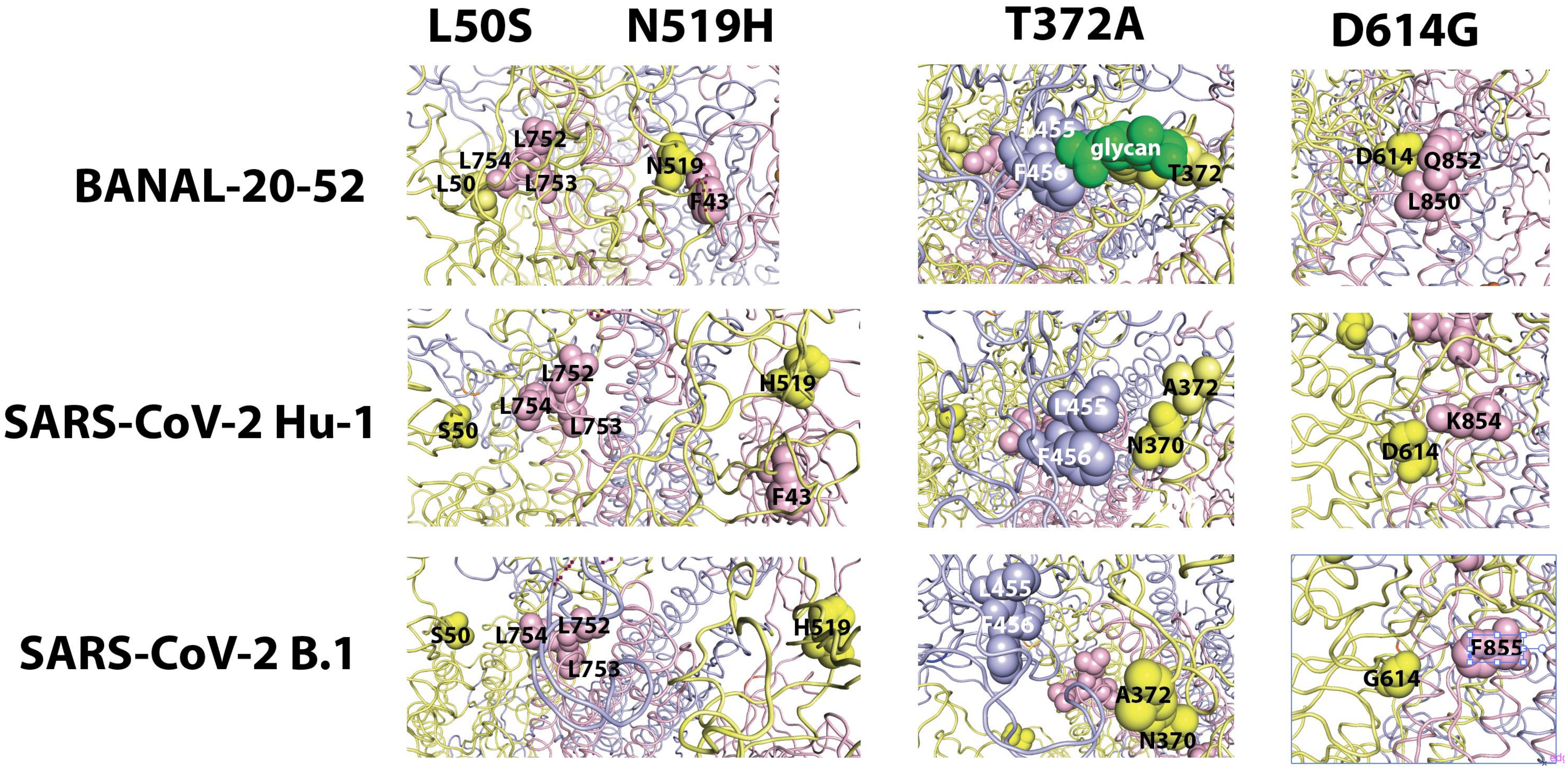
Hinges – respiratory

RBD – host range



So does D614G

The differences alter monomer interactions in Spike trimer

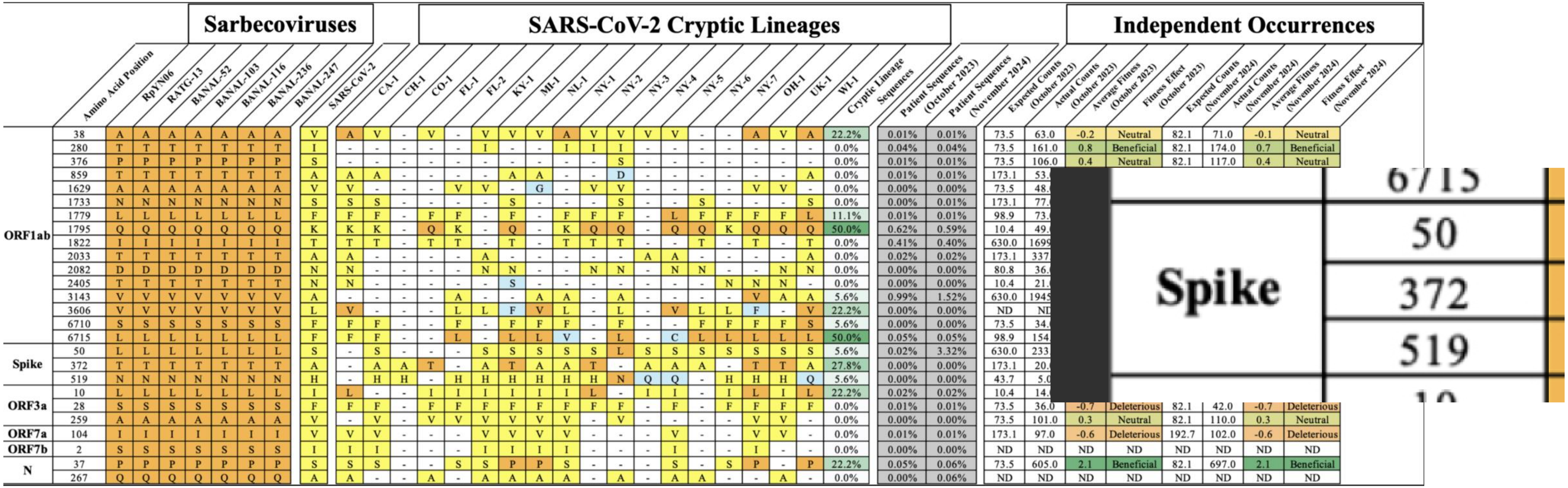


Garry, RF, Virology., Volume 614, February 2026, 110720

Detecting SARS-CoV-2 cryptic lineages using publicly available whole genome wastewater sequencing data

Reinier Suarez, Devon A. Gregory, David A. Baker, Clayton A. Rushford, Torin L. Hunter, Nicholas R. Minor, Clayton M. Russ, Emma E. Copen, David H. O'Connor, Marc C. Johnson

Version 2
Published: June 9, 2025 • https://doi.org/10.1371/journal.ppat.1012850
PLOS Pathogens



		Sarbecoviruses								SARS-CoV-2 Cryptic Lineages																					Independent Occurrences							
	Amino Acid Position	RpYN06	RATG-13	BANAL-52	BANAL-103	BANAL-116	BANAL-236	BANAL-247	SARS-CoV-2	CA-1	CH-1	CO-1	FL-1	FL-2	KY-1	MI-1	NL-1	NY-1	NY-2	NY-3	NY-4	NY-5	NY-6	NY-7	OH-1	UK-1	WI-1	Cryptic Lineage Sequences	Patient Sequences (October 2023)	Patient Sequences (November 2024)	Expected Counts (October 2023)	Actual Counts (October 2023)	Average Fitness (October 2023)	Fitness Effect (October 2023)	Expected Counts (November 2024)	Actual Counts (November 2024)	Average Fitness (November 2024)	Fitness Effect (November 2024)
ORF1ab	38	A	A	A	A	A	A	A	V	A	V	-	V	-	V	V	V	A	V	V	V	V	-	-	A	V	A	22.2%	0.01%	0.01%	73.5	63.0	-0.2	Neutral	82.1	71.0	-0.1	Neutral
	280	T	T	T	T	T	T	T	I	-	-	-	-	-	I	-	-	I	I	I	-	-	-	-	-	-	-	0.0%	0.04%	0.04%	73.5	161.0	0.8	Beneficial	82.1	174.0	0.7	Beneficial
	376	P	P	P	P	P	P	P	S	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	0.0%	0.01%	0.01%	73.5	106.0	0.4	Neutral	82.1	117.0	0.4	Neutral
	859	T	T	T	T	T	T	T	A	A	A	-	-	-	-	A	A	-	-	D	-	-	-	-	-	-	A	0.0%	0.01%	0.01%	173.1	53.						
	1629	A	A	A	A	A	A	A	V	V	-	-	-	V	V	-	G	-	V	V	-	-	-	-	V	V	-	0.0%	0.00%	0.00%	73.5	48.						
	1733	N	N	N	N	N	N	N	S	S	S	-	-	-	-	S	-	-	-	S	-	-	S	-	-	-	S	0.0%	0.00%	0.01%	173.1	77.						
	1779	L	L	L	L	L	L	L	F	F	F	-	F	F	-	F	-	F	F	F	-	L	F	F	F	F	L	11.1%	0.01%	0.01%	98.9	73.						
	1795	Q	Q	Q	Q	Q	Q	Q	K	K	K	-	Q	K	-	Q	-	K	Q	Q	-	Q	Q	K	Q	Q	Q	50.0%	0.62%	0.59%	10.4	49.						
	1822	I	I	I	I	I	I	I	T	T	T	-	T	T	-	T	-	T	T	T	-	-	T	-	T	-	T	0.0%	0.41%	0.40%	630.0	1699						
	2033	T	T	T	T	T	T	T	A	A	-	-	-	-	A	-	-	-	-	-	A	A	-	-	-	-	A	0.0%	0.02%	0.02%	173.1	337.						
	2082	D	D	D	D	D	D	D	N	N	-	-	-	-	N	N	-	-	N	N	-	N	N	-	-	N	N	0.0%	0.00%	0.00%	80.8	36.						
	2405	T	T	T	T	T	T	T	N	N	-	-	-	-	-	S	-	-	-	-	-	-	-	N	N	N	-	0.0%	0.00%	0.00%	10.4	21.						
	3143	V	V	V	V	V	V	V	A	-	-	-	-	A	-	-	A	A	-	A	-	-	-	-	V	A	A	5.6%	0.99%	1.52%	630.0	1945						
	3606	V	V	V	V	V	V	V	L	V	-	-	-	L	L	F	V	L	-	L	-	V	L	L	F	-	V	22.2%	0.00%	0.00%	ND	ND						
	6710	S	S	S	S	S	S	S	F	F	F	-	-	F	-	F	F	F	-	F	-	-	F	F	F	F	S	5.6%	0.00%	0.00%	73.5	34.						
	6715	L	L	L	L	L	L	L	F	F	F	-	-	L	-	L	L	V	-	L	-	C	L	L	L	L	L	50.0%	0.05%	0.05%	98.9	154.						
Spike	50	L	L	L	L	L	L	L	S	-	S	-	-	-	S	S	S	S	S	L	S	S	S	S	S	S	S	5.6%	0.02%	3.32%	630.0	233.						
	372	T	T	T	T	T	T	T	A	-	A	A	T	-	A	T	A	A	T	-	A	A	A	-	T	T	A	27.8%	0.00%	0.00%	173.1	20.						
	519	N	N	N	N	N	N	N	H	-	H	H	-	H	H	H	H	H	H	N	Q	Q	-	H	H	H	Q	5.6%	0.00%	0.00%	43.7	5.0						
ORF3a	10	L	L	L	L	L	L	L	I	L	-	-	I	I	I	I	I	I	L	-	I	I	-	I	L	I	L	22.2%	0.02%	0.02%	10.4	14.						
	28	S	S	S	S	S	S	S	F	F	F	-	F	F	F	F	F	F	F	F	-	F	-	F	F	F	F	0.0%	0.01%	0.01%	73.5	36.0	-0.7	Deleterious	82.1	42.0	-0.7	Deleterious
	259	A	A	A	A	A	A	A	V	-	V	-	V	V	V	V	V	V	-	V	-	-	-	-	V	V	-	0.0%	0.00%	0.00%	73.5	101.0	0.3	Neutral	82.1	110.0	0.3	Neutral
ORF7a	104	I	I	I	I	I	I	I	V	V	V	-	-	-	V	V	V	V	-	-	-	V	-	-	V	V	-	0.0%	0.01%	0.01%	173.1	97.0	-0.6	Deleterious	192.7	102.0	-0.6	Deleterious
ORF7b	2	S	S	S	S	S	S	S	I	I	I	-	-	-	I	I	I	I	-	-	-	I	-	-	I	-	-	0.0%	0.00%	0.00%	ND	ND	ND	ND	ND	ND	ND	ND
N	37	P	P	P	P	P	P	P	S	S	S	-	-	S	S	P	P	S	-	-	-	S	-	S	P	-	P	22.2%	0.05%	0.06%	73.5	605.0	2.1	Beneficial	82.1	697.0	2.1	Beneficial
	267	Q	Q	Q	Q	Q	Q	Q	A	A	-	-	A	-	A	A	A	A	-	A	-	A	A	-	-	A	-	0.0%	0.00%	0.06%	ND	ND	ND	ND	ND	ND	ND	ND

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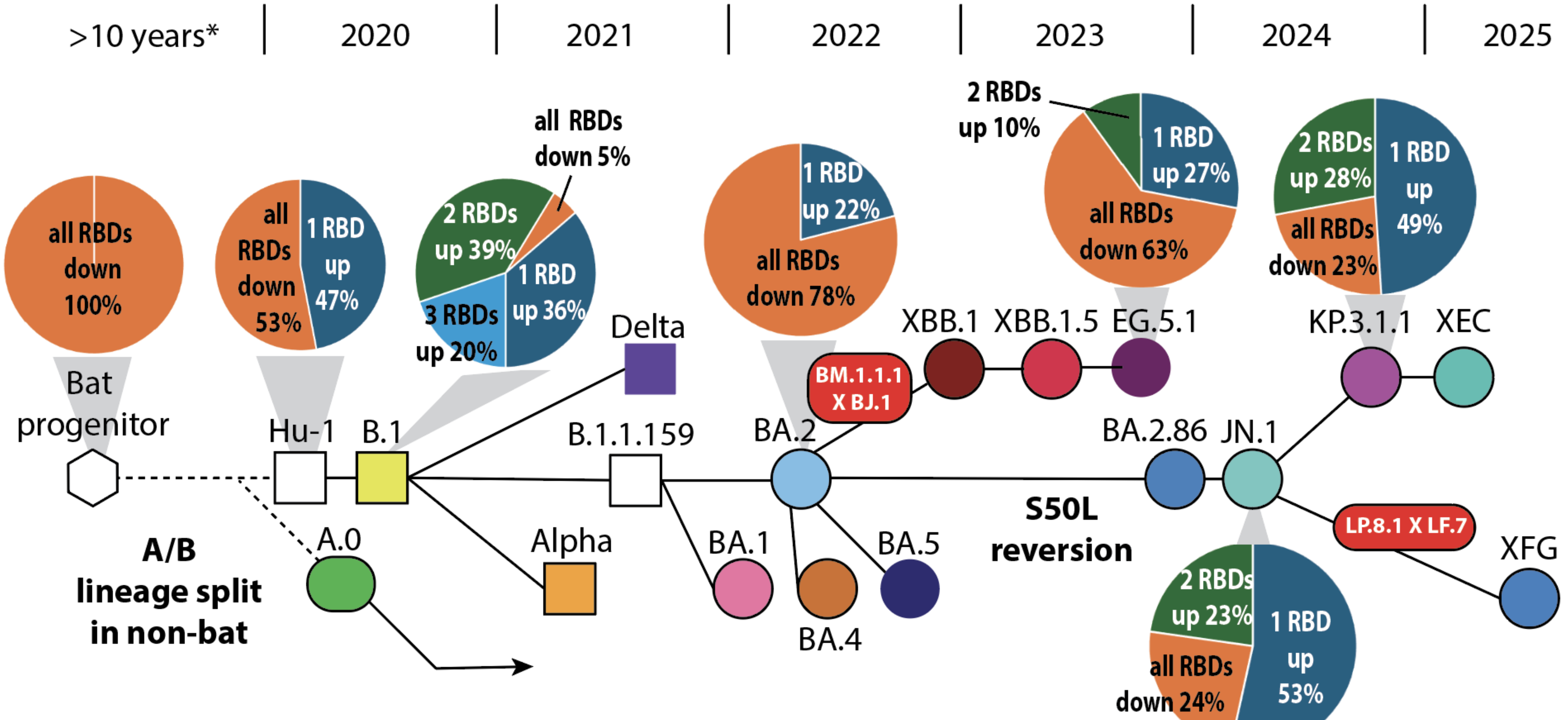
Omicron adapted for immune evasion



* Pekar et al., Cell, Volume 188, Issue 12, p3167-3183. e18June 12, 2025

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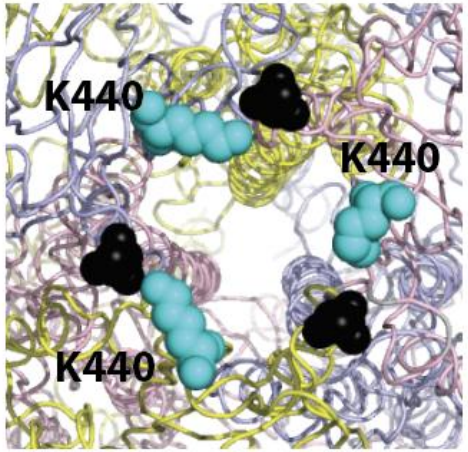
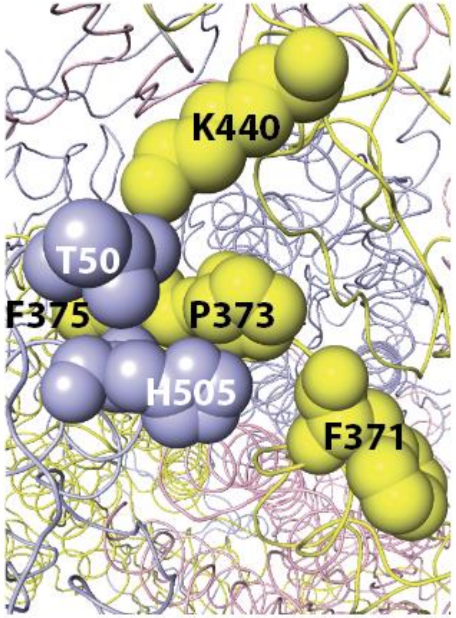


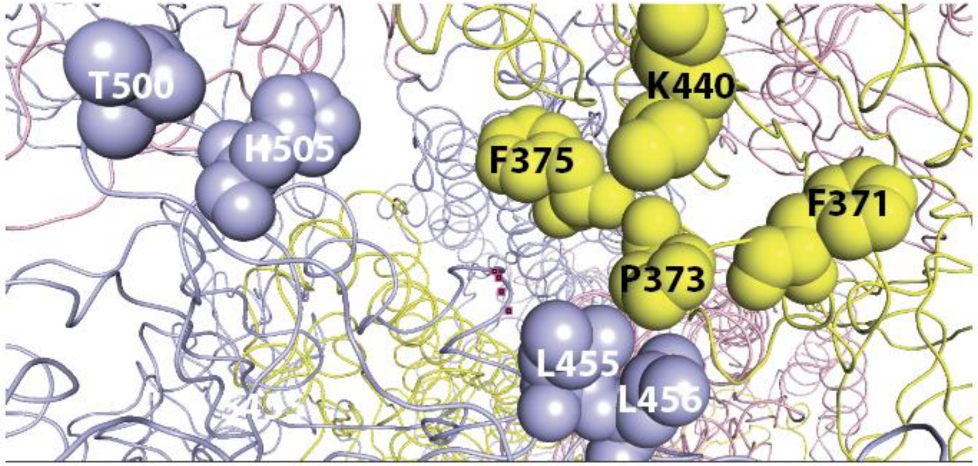
BA.2

S371F
S373P
S375F
T376A
N440K
Y505H



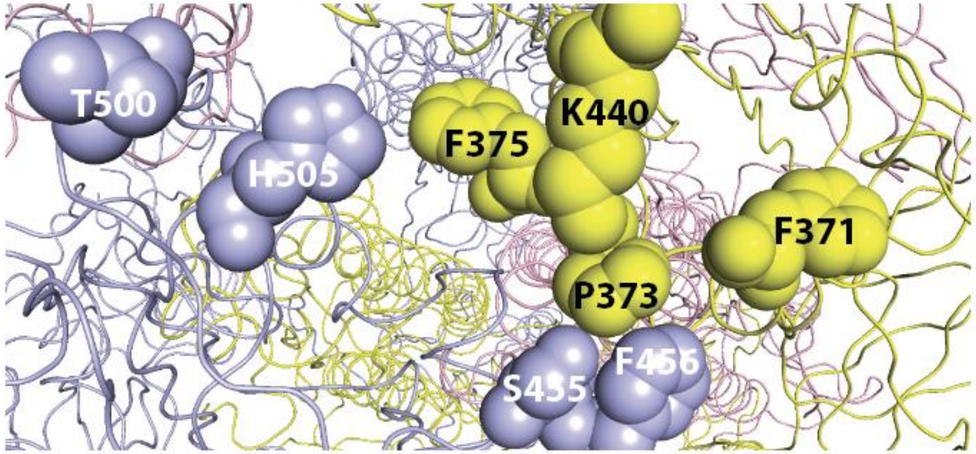
EG.5

S371F
S373P
S375F
T376A
N440K
Y505H
F456L

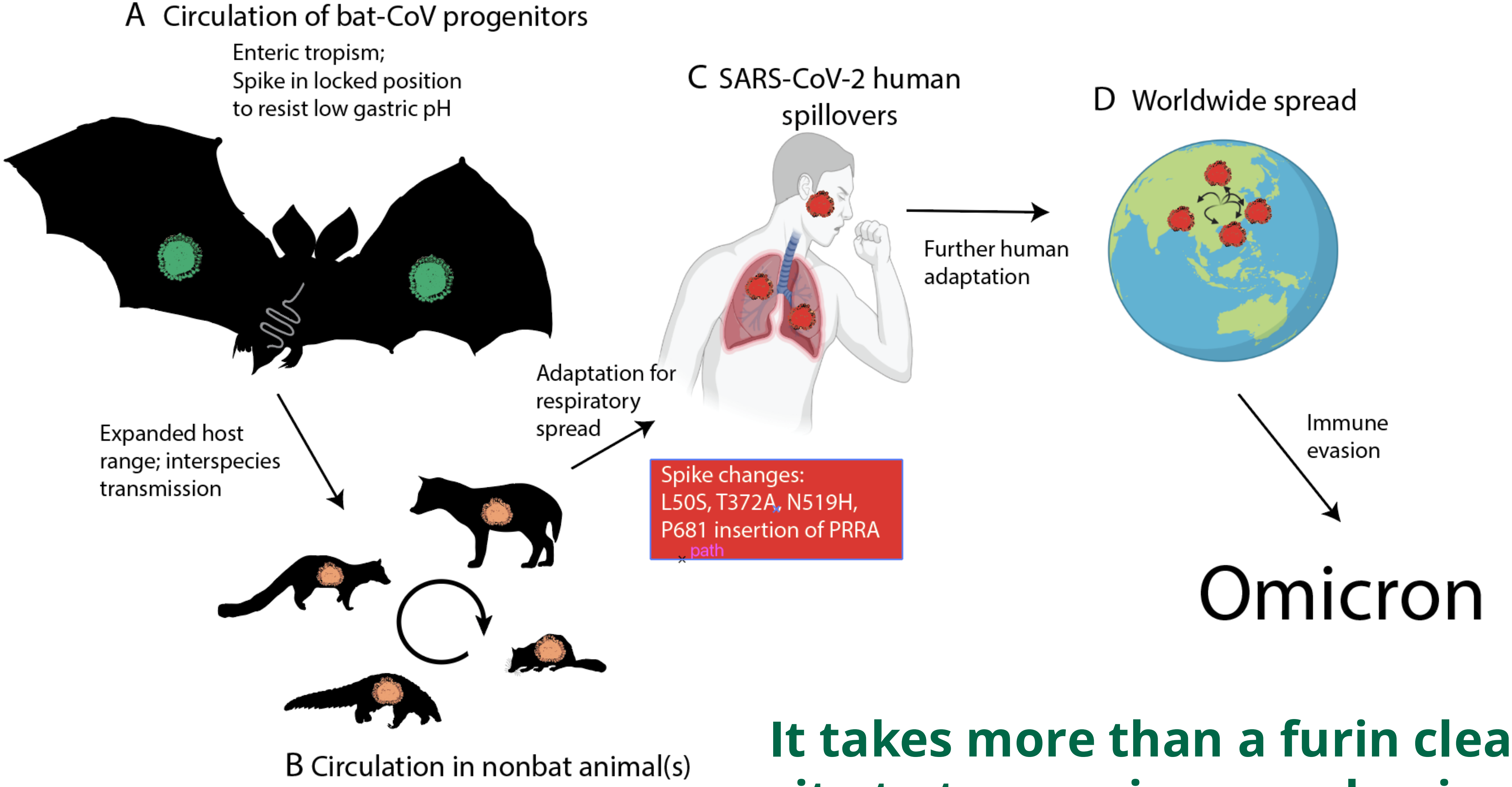


JN.1

S371F
S373P
S375F
T376A
N440K
Y505H
L455S



Omicron borrowed some old tricks using some of the same old residues such as L445 and F456 to affect Spike structural stability



A Circulation of bat-CoV progenitors

Enteric tropism;
Spike in locked position
to resist low gastric pH

Expanded host
range; interspecies
transmission

B Circulation in nonbat animal(s)

Adaptation for
respiratory
spread

C SARS-CoV-2 human
spillovers

Spike changes:
L50S, T372A, N519H,
P681 insertion of PRRA

Further human
adaptation

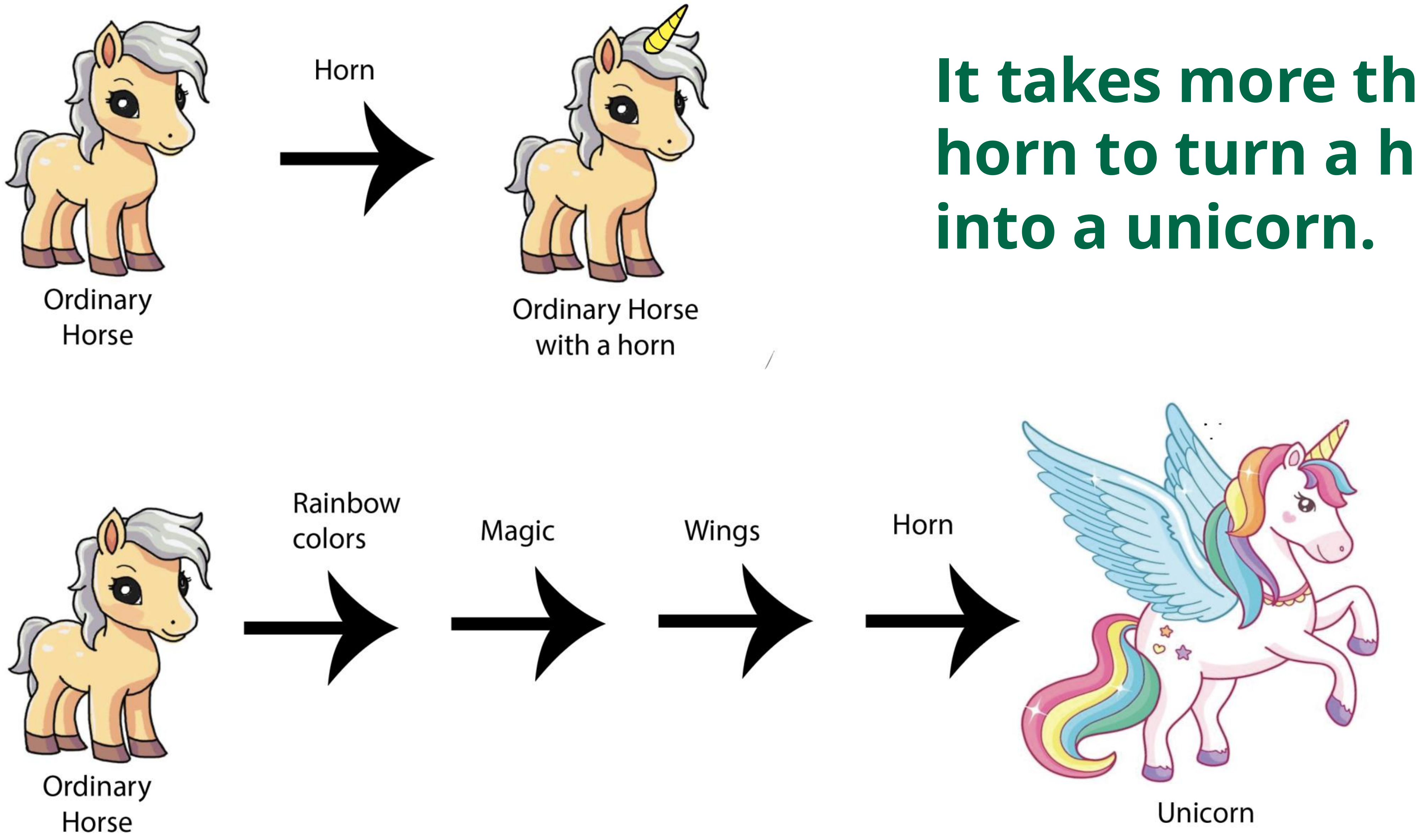
D Worldwide spread

Immune
evasion

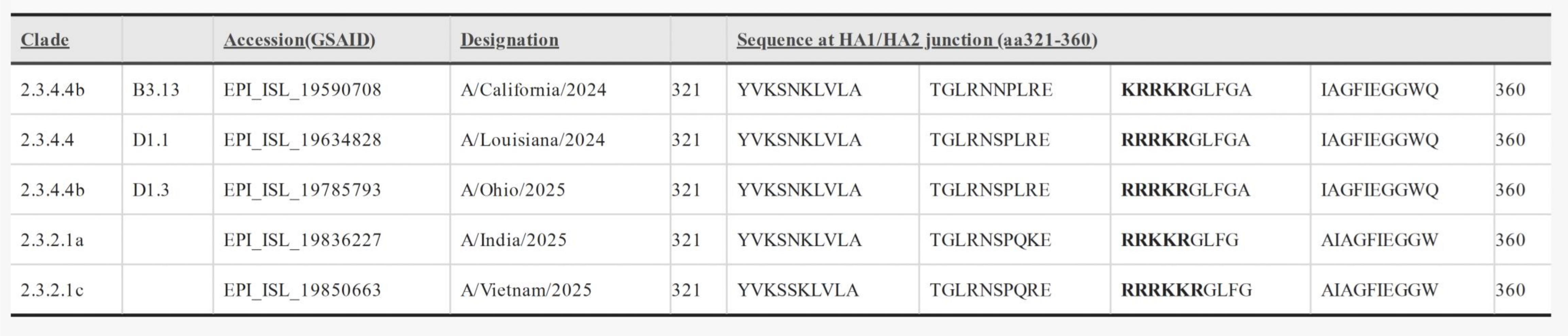
Omicron

It takes more than a furin cleavage site to turn a virus pandemic

It takes more than a horn to turn a horse into a unicorn.



Polybasic sites in current circulating strains of H5N1 Influenza virus



Clade		Accession(GSAID)	Designation		Sequence at HA1/HA2 junction (aa321-360)				
2.3.4.4b	B3.13	EPI_ISL_19590708	A/California/2024	321	YVKSNKLVLA	TGLRNNPLRE	**KRRKR**GLFGA	IAGFIEGGWQ	360
2.3.4.4	D1.1	EPI_ISL_19634828	A/Louisiana/2024	321	YVKSNKLVLA	TGLRNSPLRE	**RRRKR**GLFGA	IAGFIEGGWQ	360
2.3.4.4b	D1.3	EPI_ISL_19785793	A/Ohio/2025	321	YVKSNKLVLA	TGLRNSPLRE	**RRRKR**GLFGA	IAGFIEGGWQ	360
2.3.2.1a		EPI_ISL_19836227	A/India/2025	321	YVKSNKLVLA	TGLRNSPQKE	**RRKKR**GLFG	AIAGFIEGGW	360
2.3.2.1c		EPI_ISL_19850663	A/Vietnam/2025	321	YVKSSKLVLA	TGLRNSPQRE	**RRRKKR**GLFG	AIAGFIEGGW	360

Circulating H5N1 bird/cow influenza viruses have furin cleavage site but it will take additional changes to make them pandemic

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ANNUAL REVIEW OF VIROLOGY **Volume 10, 2023**

Review Article | **Open Access**

Influenza: Searching for Pandemic Origins

Robert G. Webster[1]

Hide Affiliations and Author Notes

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Vol. 10:1-23 (Volume publication date September 2023) | **https://doi.org/10.1146/annurev-virology-111821-125223**

> "Subsequent studies established that:
>
> (*a*) aquatic birds are a natural reservoir of influenza A viruses,
>
> (*b*) these viruses replicate primarily in cells lining the intestinal tract,
>
> (*c*) reassortment in nature can lead to novel pandemic influenza viruses, and
>
> (*d*) live bird markets are one place where transmission of influenza virus from animals to humans occurs."