How human protein adapt in response to viruses? Altering protein stability as a major mechanism

Chenlu Di[1,2](cdi@ucla.edu), Jesús murga moreno[1,3], David Enard[1]

1. University of Arizona 2. University of California, Los Angeles 3. Universitat Autònoma de Barcelona

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@DiChenlu
cdi@.ucla.edu

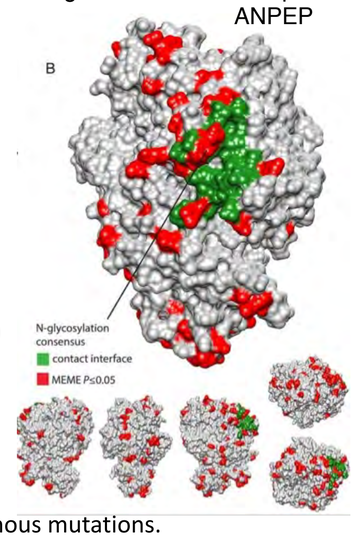
How human protein adapt in response to viruses?

Key human proteins in the process: **VIPs** (virus-interacting proteins), that are host proteins that interacts with viral protein.

Previous findings in VIPs: large number of adaptive substitutions (α =27%) in host virus-interacting proteins (VIPs) (Fig.1 modified from Enard, 2016).

Limitation: Fig.1 Limited interface (blue) vs. large number of adaptive substitution (red)

Fig. 1 coronavirus receptor ANPEP



Hypothesis: Adaptation to past viral infections happened through changing protein stabilities in virus-interacting proteins.

Protein stability: correlates with the amount of corrected folded protein

LSC: mutations that cause large stability changes; might have larger fitness effects through changing protein stability
SSC: mutations that cause small stability changes

Fig.2 Distribution of protein stability changes caused by non-synonymous mutations.

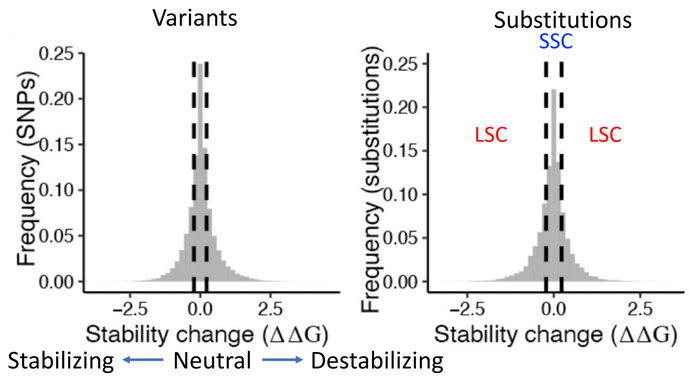


Fig.2 Left: variants from 1KGP phase3 AFR. Right: substitutions in human lineage.

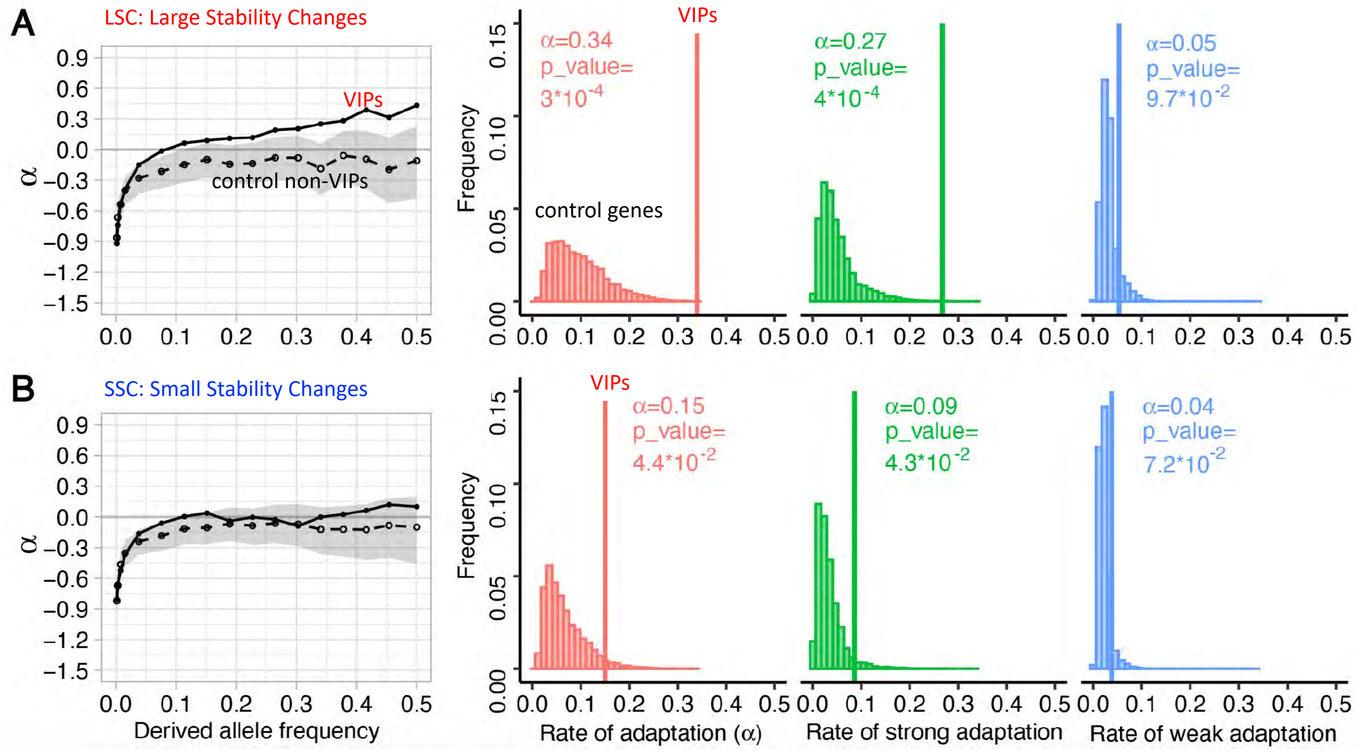
Conclusion: Stability evolution and thus functional host protein abundance evolution, was a prominent mechanism of host protein adaptation during viral epidemics in humans.

Key results:

1. Most of the adaptative substitutions attributable to viruses in VIPs largely changed stability.
2. Increased adaptation through large stability changes in more RNA than DNA viruses.
3. The stability of immune VIPs had changed more than expected, indicating directional selection.
4. The stability of pro-viral VIPs had changed less than expected, indicating compensatory selection.

Results

1. Higher rate of adaptation (α) in mutations that largely changed protein stability.



Tables: Count the number of adaptive substitutions in VIPs and control non-VIPs

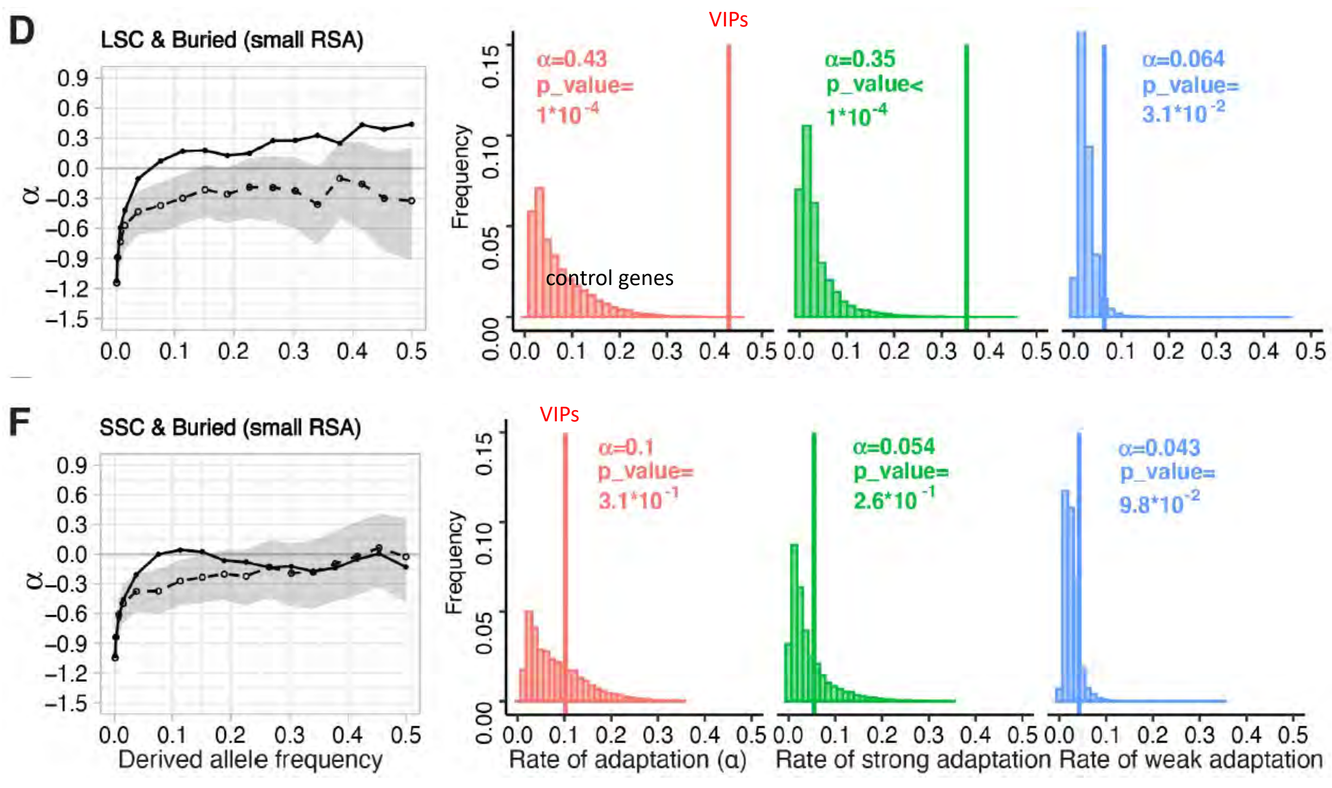
	VIPs-LSCs	VIPs-SSCs
number of non-synonymous substitution (Dn)	737	832
adaptation rate (α)	34% (fig.1A)	15% (fig.1B)
adaptive substitutions (Dn-α)	250	125
proportion of Dn-α in VIPs-LSCs= 250/(250+125)=67%		

	nonVIPs-LSCs	nonVIPs-SSCs
adaptation rate	8%	8%

VIPs - nonVIPs= VIPs (attributable to viruses)

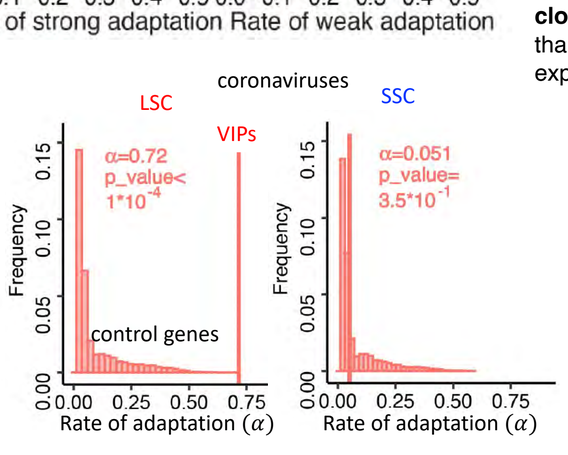
	VIPs-LSCs	VIPs-SSCs
α	34%-8%=26%	15%-8%=7%
Dn-α	26%*737=192	7%*737=58
proportion of Dn-α attribute to viruses in VIPs-LSCs= 192/(192+58)=77%		

2. Stability explains increased VIP adaptation at buried residues



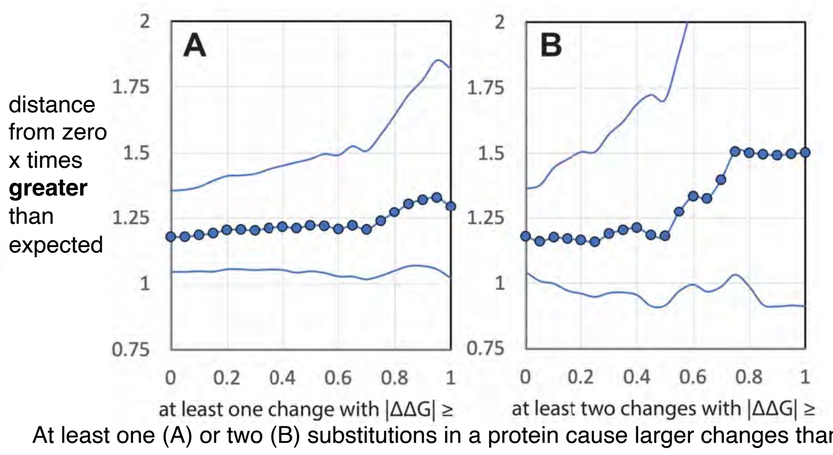
3. RNA viruses and coronaviruses

	LSC					SSC				
	α	α_s	α_w	DN	DN-α	α	α_s	α_w	DN	DN-α
RNA only	0.40	0.31	0.06	286	114.16	0.04	0.02	0.01	339	13.73
DNA only	0.11	0.04	0.04	137	14.45	0.04	0.01	0.02	139	5.02



4. Directional selection in immune VIPs and compensatory adaptation in non-immune VIPs

Directional evolution in immune antiviral VIPs



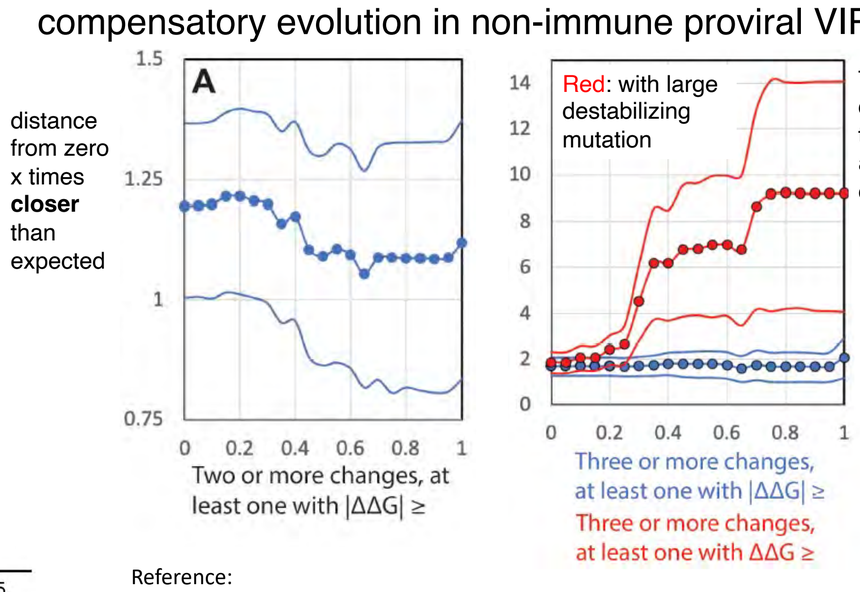
The per-protein stability change is away from zero than expected if proteins are under directional evolution.

y-axis is how many times the per-VIP stability changes is larger than expected. The larger, the stronger evidence for directional selection.

Middle curve is the average, up and low curves are 95% confidence interval of 1,000,000 repeats.

At least one (A) or two (B) substitutions in a protein cause larger changes than the value in x-axis:

compensatory evolution in non-immune proviral VIPs.



The per-protein stability change is closer to zero than expected if proteins are under compensatory evolution.

Blue: Same thresholds of stability changes but include both stabilizing and destabilizing changes

Reference:
Stability evolution as a major mechanism of human protein adaptation in response to viruses
Chenlu Di, Jesus Murga-Moreno, David Enard
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