LETTER TO THE EDITOR

Commentary on "Poor evidence for host-dependent regular RNA editing in the transcriptome of SARS-CoV-2"

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Abstract

Analysis of the SARS-CoV-2 transcriptome has revealed a background of low-frequency intra-host genetic changes with a strong bias towards transitions. A similar pattern is also observed when inter-host variability is considered. We and others have shown that the cellular RNA editing machinery based on ADAR and APOBEC host-deaminases could be involved in the onset of SARS-CoV-2 genetic variability. Our hypothesis is based both on similarities with other known forms of viral genome editing and on the excess of transition changes, which is difficult to explain with errors during viral replication. Zong et al. criticize our analysis on both conceptual and technical grounds. While ultimate proof of an involvement of host deaminases in viral RNA editing will depend on experimental validation, here, we address the criticism to suggest that viral RNA editing is the most reasonable explanation for the observed intra- and inter-host variability.

Keywords ADARs · APOBECs · Viruses · RNA editing

Main Text

We and others have hypothesized that the genetic information of the SARS-CoV-2 could be affected by the cellular RNA editing machinery based on the ADAR and APOBEC proteins. The hypothesis originates from two observations: (a) several viral genomes show mutational patterns that could be ascribed to the activity of host deaminases (Cattaneo et al. 1988; Vartanian et al. 1991; Harris et al. 2003; Mahieux et al. 2005; Noguchi et al. 2005; Taylor et al. 2005; Zahn et al. 2007; Phuphuakrat et al. 2008; Vartanian 2008; Carpenter et al. 2009; Doria et al. 2009, 2011; George et al. 2009; Clerzius et al. 2011; Pfaller et al. 2011; Suspene et al.

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2011; Samuel 2012; Cuevas et al. 2015; Tomaselli et al. 2015; Peretti et al. 2018; Rosani et al. 2019)—this has been confirmed experimentally in several cases—and (b) there is an excess of transition changes occurring both at the intra-host (Di Giorgio et al. 2020; Farkas et al. 2020; Popa et al. 2020; Wang et al. 2021; Graudenzi et al. 2021; Gregori et al. 2021; Lythgoe et al. 2021; Song et al. 2021; Tonkin-Hill et al. 2021; Voloch et al. 2021; Picardi and Mansi 2022) and inter-host scale (Simmonds 2020; van Dorp et al. 2020; Jacob-Hirsch et al. 2020; Klimczak et al. 2020; Kosuge et al. 2020; Mourier et al. 2020; Popa et al. 2020; Azgari et al. 2021; Deng et al. 2021; Rice et al. 2021; Sadykov et al. 2021; Simmonds and Azim Ansari 2021; Tasakis et al. 2021; Matyášek et al. 2021; Pang et al. 2021; Ramazzotti et al. 2021). Such excess is not explainable with the known mutational pattern introduced by the RNA-dependent RNA polymerase or by the SARS-CoV-2 proofreading machinery (Smith et al. 2013; Kabinger et al. 2021). It is still not clear whether the involvement of the cellular RNA editing machinery affects the onset/progression of the COVID-19 infection. On the other hand, the outcomes of such editing heavily skew the evolutionary trajectory of the virus (Simmonds 2020; van Dorp et al. 2020; Jacob-Hirsch et al. 2020; Klimczak et al. 2020; Kosuge et al. 2020; Mourier et al. 2020; Popa et al. 2020; Azgari et al. 2021; Deng et al. 2021; Sadykov et al. 2021; Simmonds and Azim Ansari 2021;

Tasakis et al. 2021; Matyášek et al. 2021; Pang et al. 2021; Ramazzotti et al. 2021).

As currently available studies are all based on mutational analyses of the viral genome/transcriptome, we wholeheartedly agree with Zong et al. (2022) that final proof of ADAR and APOBEC involvement will be only obtained through genetic analysis, by infecting ADAR- and APOBEC-deficient cells with the SARS-CoV-2 virus.

Zong et al. (2022) criticize our analysis based on both conceptual and technical grounds and we think it is useful to address the criticism in order to clarify the issues for future studies. Here, we address their criticism following the order outlined in their abstract:

(1) **No prediction of what the mutation profile should be.**

The authors suggest we did not have a null hypothesis against which to test the possibility of RNA editing in the viral transcriptomes. This probably depends from their misunderstanding of our analysis: they compare our claims to those presented in a report that hypothesized that every possible type of RNA–DNA mismatch could represent a post-transcriptional modification in the human transcriptome (Li et al. 2012). Our scope was far more limited, as we just wanted to see whether ADAR and APOBEC editing, the only well-characterized RNA modifications easily identifiable by direct sequencing, could represent a source of variability in the virus.

With this aim, our expectations were quite clear: if RNA editing by ADARs and/or APOBECs plays a role in intra-host diversification of the virus; A > G / T > C and C > T / G > A substitutions should outnumber all other types. This is quite evident from the mutational patterns observed, both in our and in other follow-up analyses (Farkas et al. 2020; Simmonds 2020; van Dorp et al. 2020; Klimczak et al. 2020; Kosuge et al. 2020; Azgari et al. 2021; Pathak et al. 2021; Ramazzotti et al. 2021; Rice et al. 2021; Sadykov et al. 2021; Simmonds and Azim Ansari 2021; Song et al. 2021; Tasakis et al. 2021; Tonkin-Hill et al. 2021; Friedman et al. 2021; Voloch et al. 2021; Wang et al. 2021; Graudenzi et al. 2021; Gregori et al. 2021; Lythgoe et al. 2021; Matyášek et al. 2021; Pang et al. 2021; Picardi and Mansi 2022). Furthermore, even though the intra-host single-nucleotide polymorphism (SNV) pattern might be questionable due to sequencing errors, we observed a similar enrichment also in inter-host SNVs from SARS-CoV-2 genomic sequences, which has been confirmed by further studies, including those using more refined approaches (i.e., mutational signatures (Popa et al. 2020; Graudenzi et al. 2021). Based on this parallelism, it is sensible to hypothesize that

some RNA sites that are edited eventually become fixed in the viral genome.

Considering that similar results—using different pipelines and datasets—have been found in all intra- and inter-host analyses published so far, the authors' claim that the "obtained a mutation spectrum similar to the random mismatch spectrum" is quite wrong. Especially wrong since the authors take our argument about "transitions and transversions" out of context and do not realize that we actually had a mutational pattern against which to compare our analysis: past mutational analyses of SARS-CoV (Fig. 4A-B Smith et al. 2013) show that both the viral replication machinery (both transcription and proofreading system) have a mutational profile quite different from what we observed in the COVID-19 samples—notably with a bias towards transversions. The infected cells used in these analyses were Vero cells, a line where APOBECs are not active (ADARs and APOBECs induce transitions).

While we could not expect a defined amount of adenine-to-inosine or cytosine-to-uracil editing beforehand, we think that our expectations were somehow more realistic than those advanced by the authors themselves with their prediction that "a successful RNA editing paper would find an extremely high A > G% (usually > 80%) after multiple steps of filters". Such expectation relies entirely on the assumption that the effects of RNA editing on the viral transcriptome should strictly mirror those observed in the human one. Such expectation completely disregards the potential effects of other RNA editing enzymes such as the APOBECs or replication-dependent errors.

For example, the mutational pattern in HIV is biased towards G > A mutations as its genome is targeted mainly by APOBECs during the first cDNA synthesis stage of reverse transcription (e.g., (Harris et al. 2003)). Analogously, any mutational pattern observed will depend on the different mutational processes acting on the virus.

(2) **Filtering steps and cutoffs in their pipeline failed to increase the A > G percentage, neither did they change the mismatch profile.**

As the authors state, in a metatranscriptomic context, the only viable strategy for discriminating sequencing errors from real SNVs is to apply post-filtering approaches. Indeed, the filter on the allelic fraction (> 0.005), not mentioned by the authors, significantly increases the signal-to-noise ratio, increasing the fraction of A > G / T > C and C > T / G > A substitutions. We agree that this can be further optimized and, indeed, subsequent studies proposed more refined approaches to reduce the number of false positive calls (e.g., (Picardi and Mansi 2022)). It is indeed reassuring that dif-

ferent pipelines converged to the same conclusions (Di Giorgio et al. 2020; Farkas et al. 2020; Popa et al. 2020; Wang et al. 2021; Graudenzi et al. 2021; Gregori et al. 2021; Lythgoe et al. 2021; Pathak et al. 2021; Song et al. 2021; Tonkin-Hill et al. 2021; Voloch et al. 2021).

While we agree that the mutational spectrum is not significantly affected by the filters reanalyzed by Zong et al. (2022), these filters were nonetheless necessary to avoid introducing bias in the estimation of the allelic fraction of the observed changes.

Low coverage positions (< 20) with few supporting reads (< 4) would artificially inflate the allelic frequency of these low confidence substitutions (e.g., at a position with a coverage of 20 reads, even a single mutated read would result in a 0.05 allelic fraction, way higher than the threshold we set to consider a SNV). Considering the high heterogeneity in terms of coverage, within and among samples, we used this filter to get a better view on the distribution of allelic frequencies. This is important to direct the interpretation of the data, as different thresholds can be used to arbitrarily discriminate 'RNA editing' positions from 'germline' variants based on allelic fraction. This allowed us to find the similarity between the proposed editing of the viral transcriptome and what happens in the cellular RNA editing: not high levels of editing on a few selected residues, which would quickly affect the evolution of the virus, but low-frequency editing, reminiscent of what happens mostly on Alu sequences (0.6% average frequency, what the authors call hyperediting) (Porath et al. 2014; Picardi and Pesole 2020). Sequencing errors at the read ends typically introduce false positive SNVs, as the authors state, and are the reason for applying the 15 bp padding filter to the read ends. While not substantially changing the mutational profile, the filter was needed to avoid introduction of SNVs from recurrent errors at the read ends. These false positives would have weighted our analysis on the consequences of editing at synonymous/nonsynonymous sites. Of course, a proper analysis should be carried out not on intra-host changes—which are not selected—but on inter-host ones, as they are the result of selection. Even if the authors claim we did not, we have indeed analyzed it (our supplementary 2 table), but we did not weight much on it because the dataset was too small. Indeed, subsequent studies, very thorough and expertly argumented have been carried out by others, and all of them concurred that RNA editing is likely to be a major factor in determining the evolutionary trajectory of the SARS-CoV-2 (e.g., (Simmonds 2020; Rice et al. 2021; Simmonds and Azim Ansari 2021)). It should also be taken into account that, beside the evolutionary significance of the outcomes of RNA editing, the biological significance of the editing of the viral transcriptome might lie more on the cellular response to the infection than on the recoding effects of the editing.

(3) **Failure in interpreting the equally-abundant T > C substitutions.**

(4) **ADAR motifs and RNA structures contradicted with the antisense editing proposed by themselves.**

In our paper, we hypothesize that both A > G and T > C polymorphisms derive from ADAR activity editing during viral replication, when positive and negative strands coexist—by necessity—as double-stranded RNA: as ADARs induce adenine-to-inosine changes, these will appear as A > G when the positive strand is targeted and as T > C when the negative strand is transcribed back to positive. We think it is a fairly reasonable model, as the authors themselves admit after their explanation on how true T > C polymorphisms in the human transcriptome cannot originate from ADAR editing (which targets only adenines).

Indeed, we never propose that ADAR editing could target thymines in the viral transcriptome, which would be problematic, as there are no thymines in RNA. And we have been very careful in differentiating the biological phenomenon (A-to-I, C-to-U) from the analytical details (A > G, T > C, C > T, and G > A) of the bioinformatic analysis.

It is true that we did not discuss a possible clash between the transcription complex and the ADARs ability to target dsRNA, but there was no reason for it: ADARs could target double-stranded RNA at any time after the transcription complex leaves the scene. On the other hand, we apologize for not specifying something we thought it was obvious: when analyzing the editing sequence contexts, we have used the reverse complement to analyze T > C changes together with A > G ones, as evident from sequence logos—where the central position is always an A.

(5) **ADARs should be poorly expressed in cytosol compared to APOBECs.**

RNA editing of the human transcriptome typically takes place in the nucleus. This is something that has been experimentally established for all well-characterized RNA editing events, be they dependent on ADARs (e.g., (Patterson and Samuel 1995; Behm et al. 2017) or on APOBEC1 (e.g., (Lau et al. 1991; Sowden et al. 1996). Yet, localization of both APOBECs and ADARs is not limited to the nucleus (e.g., (Patterson and Samuel 1995; Yang et al. 2001; Bennett et al. 2006; Land et al. 2013) and even nuclear proteins are synthesized in the cytoplasm and shuttle through it. While the significance of ADAR editing in the cytoplasm has never been experimentally characterized, its cytoplasmic

localization alters the fate of short interfering RNAs (Yang et al. 2005). Based on this, cytoplasmic editing is conceivable also for ADARs.

Eventually, it is probable that the amount of cytoplasmic editing and its effects are likely determined by the cellular milieu (presence/absence of cytoplasmic ADAR1 isoform, APOBEC expression, etc.) and we agree that wet-lab studies are needed to understand the relevance of RNA editing in viral infections, including those originating from SARS-CoV-2.

Nonetheless, we find that the statement "we only propose that those editing sites are unreliable (likely to be replication errors) but we do not claim that none of the sites they found are true editing sites" is quite a weak foreword for a manuscript that ends with the "findings and conclusions made by Di Giorgio et al. were erroneous and misleading and should be correctly in instant"…

Declarations

References

Azgari C, Kilinc Z, Turhan B, et al (2021) The mutation profile of sars-cov-2 is primarily shaped by the host antiviral defense. Viruses 13. https://doi.org/10.3390/v13030394

Behm M, Wahlstedt H, Widmark A et al (2017) Accumulation of nuclear ADAR2 regulates adenosine-to-inosine RNA editing during neuronal development. J Cell Sci 130:745–753. https://doi.org/10.1242/jcs.200055

Bennett RP, Diner E, Sowden MP et al (2006) APOBEC-1 and AID are nucleo-cytoplasmic trafficking proteins but APOBEC3G cannot traffic. Biochem Biophys Res Commun 350:214–219. https://doi.org/10.1016/j.bbrc.2006.09.032

Carpenter JA, Keegan LP, Wilfert L et al (2009) Evidence for ADAR-induced hypermutation of the Drosophila sigma virus (Rhabdoviridae). BMC Genet 10:1–7. https://doi.org/10.1186/1471-2156-10-75

Cattaneo R, Schmid A, Eschle D et al (1988) Biased hypermutation and other genetic changes in defective measles viruses in human brain infections. Cell 55:255–265. https://doi.org/10.1016/0092-8674(88)90048-7

Clerzius G, Gélinas JF, Gatignol A (2011) Multiple levels of PKR inhibition during HIV-1 replication. Rev Med Virol 21:42–53. https://doi.org/10.1002/rmv.674

Cuevas JM, Geller R, Garijo R et al (2015) Extremely High Mutation Rate of HIV-1 In Vivo. PLoS Biol 13:1–19. https://doi.org/10.1371/journal.pbio.1002251

Deng S, Xing K, He X (2021) Mutation signatures inform the natural host of SARS-CoV-2. bioRxiv. https://doi.org/10.1101/2021.07.05.451089

Di Giorgio S, Martignano F, Torcia MG et al (2020) Evidence for host-dependent RNA editing in the transcriptome of SARS-CoV-2. Sci Adv 6:1–9. https://doi.org/10.1126/sciadv.abb5813

Doria M, Neri F, Gallo A et al (2009) Editing of HIV-1 RNA by the double-stranded RNA deaminase ADAR1 stimulates viral infection. Nucleic Acids Res 37:5848–5858. https://doi.org/10.1093/nar/gkp604

Doria M, Tomaselli S, Neri F et al (2011) ADAR2 editing enzyme is a novel human immunodeficiency virus-1 proviral factor. J Gen Virol 92:1228–1232. https://doi.org/10.1099/vir.0.028043-0

Farkas C, Mella A, Haigh JJ (2020) Large-scale population analysis of SARS-CoV-2 whole genome 1 sequences reveals host-mediated viral evolution with emergence of mutations 2 in the viral Spike protein associated with elevated mortality rates. medRxiv 2020.10.23.20218511

Friedman N, Jacob-Hirsch J, Drori Y et al (2021) Transcriptomic profiling and genomic mutational analysis of human coronavirus (HCoV)-229E -infected human cells. PLoS ONE 16:1–15. https://doi.org/10.1371/journal.pone.0247128

George CX, Li Z, Okonski KM et al (2009) Tipping the balance: antagonism of pkr kinase and adar1 deaminase functions by virus gene products. J Interf Cytokine Res 29:477–487. https://doi.org/10.1089/jir.2009.0065

Graudenzi A, Maspero D, Angaroni F et al (2021) Mutational signatures and heterogeneous host response revealed via large-scale characterization of SARS-CoV-2 genomic diversity. iScience 24:102116. https://doi.org/10.1016/j.isci.2021.102116

Gregori J, Cortese MF, Piñana M et al (2021) Host-dependent editing of SARS-CoV-2 in COVID-19 patients. Emerg Microbes Infect 10:1777–1789. https://doi.org/10.1080/22221751.2021.1969868

Harris RS, Bishop KN, Sheehy AM et al (2003) DNA deamination mediates innate immunity to retroviral infection. Cell 113:803–809

Jacob-Hirsch J, Drori Y, Eran E, et al (2020) Transcriptomic profiling of human corona virus (HCoV)-229E-infected human 2 cells and genomic mutational analysis of HCoV-229E and SARS-CoV-2 3 4 Nehemya. bioRxiv 2020.08.17.253682

Kabinger F, Stiller C, Schmitzová J et al (2021) Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol 28:740–746. https://doi.org/10.1038/s41594-021-00651-0

Klimczak LJ, Randall TA, Saini N et al (2020) Similarity between mutation spectra in hypermutated genomes of rubella virus and in SARS-CoV-2 genomes accumulated during the COVID-19 pandemic. PLoS ONE 15:1–21. https://doi.org/10.1371/journal.pone.0237689

Kosuge M, Furusawa-Nishii E, Ito K et al (2020) Point mutation bias in SARS-CoV-2 variants results in increased ability to stimulate inflammatory responses. Sci Rep 10:1–10. https://doi.org/10.1038/s41598-020-74843-x

Land AM, Law EK, Carpenter MA et al (2013) Endogenous APOBEC3A DNA cytosine deaminase is cytoplasmic and non-genotoxic. J Biol Chem 288:17253–17260. https://doi.org/10.1074/jbc.M113.458661

Lau PP, Xiong W, Zhu HJ et al (1991) Apolipoprotein B mRNA editing is an intranuclear event that occurs posttranscriptionally coincident with splicing and polyadenylation. J Biol Chem 266:20550–20554. https://doi.org/10.1016/s0021-9258(18)54960-7

Li M, Wang IX, Li Y, et al (2012) Widespread RNA and DNA sequence differences in the human transcriptome. Science (80-) 335:. https://doi.org/10.1126/science.1210624

Lythgoe KA, Hall M, Ferretti L, et al (2021) SARS-CoV-2 within-host diversity and transmission. Science (80-) 372:. https://doi.org/10.1126/SCIENCE.ABG0821

Mahieux R, Suspène R, Delebecque F et al (2005) Extensive editing of a small fraction of human T-cell leukemia virus type 1 genomes by four APOBEC3 cytidine deaminases. J Gen Virol 86:2489–2494. https://doi.org/10.1099/vir.0.80973-0

Matyášek R, Řehůřková K, Marošiová KB, Kovařík A (2021) Mutational asymmetries in the sars-cov-2 genome may lead to increased hydrophobicity of virus proteins. Genes (Basel) 12. https://doi.org/10.3390/genes12060826

Mourier T, Sadykov M, Carr MJ, et al (2020) Host-directed editing of the SARS-CoV-2 genome. Biochem Biophys Res Commun. https://doi.org/10.1016/j.bbrc.2020.10.092

Noguchi C, Ishino H, Tsuge M et al (2005) G to A hypermutation of hepatitis B virus. Hepatology 41:626–633. https://doi.org/10.1002/hep.20580

Pang X, Li P, Zhang L et al (2021) Emerging severe acute respiratory syndrome coronavirus 2 mutation hotspots associated with clinical outcomes and transmission. Front Microbiol 12:1–12. https://doi.org/10.3389/fmicb.2021.753823

Pathak AK, Mishra GP, Uppili B, et al (2021) Spatio-temporal dynamics of intra-host variability in SARS-CoV-2 genomes. bioRxiv 837–846. https://doi.org/10.1101/2020.12.09.417519

Patterson JB, Samuel CE (1995) Expression and regulation by interferon of a double-stranded-RNA-specific adenosine deaminase from human cells: evidence for two forms of the deaminase. Mol Cell Biol 15:5376–5388. https://doi.org/10.1128/mcb.15.10.5376

Peretti A, Geoghegan EM, Pastrana DV et al (2018) Characterization of BK polyomaviruses from kidney transplant recipients suggests a role for APOBEC3 in driving in-host virus evolution. Cell Host Microbe 23:628-635.e7. https://doi.org/10.1016/j.chom.2018.04.005

Pfaller CK, Li Z, George CX, Samuel CE (2011) Protein kinase PKR and RNA adaenosine deaminase ADAR1: new roles for old players as modulators of the interferon response. Curr Opin Immunol 23:573–582. https://doi.org/10.1016/j.coi.2011.08.009.Protein

Phuphuakrat A, Kraiwong R, Boonarkart C et al (2008) Double-stranded RNA adenosine deaminases enhance expression of human immunodeficiency virus type 1 proteins. J Virol 82:10864–10872. https://doi.org/10.1128/jvi.00238-08

Picardi E, Mansi L (2022) Detection of A-to-I RNA editing in SARS-COV-2. 1–13

Picardi E, Pesole G (2020) RNA editing - methods and protocols

Popa A, Genger JW, Nicholson MD et al (2020) Genomic epidemiology of superspreading events in Austria reveals mutational dynamics and transmission properties of SARS-CoV-2. Sci Transl Med 12:1–13. https://doi.org/10.1126/scitranslmed.abe2555

Porath HT, Carmi S, Levanon EY (2014) A genome-wide map of hyper-edited RNA reveals numerous new sites. Nat Commun 5:1–10. https://doi.org/10.1038/ncomms5726

Ramazzotti D, Angaroni F, Maspero D, et al (2021) Large-scale analysis of synonymous viral variants reveals global adaptation of the SARS-CoV-2 to the human codon usage. bioRxiv 2021.04.23.441151

Rice AM, Castillo Morales A, Ho AT et al (2021) Evidence for strong mutation bias toward, and selection against, U content in SARS-CoV-2: implications for vaccine design. Mol Biol Evol 38:67–83. https://doi.org/10.1093/molbev/msaa188

Rosani U, Bai CM, Maso L et al (2019) A-to-I editing of Malacoherpesviridae RNAs supports the antiviral role of ADAR1 in mollusks. BMC Evol Biol 19:1–18. https://doi.org/10.1186/s12862-019-1472-6

Sadykov M, Mourier T, Guan Q, Pain A (2021) Short sequence motif dynamics in the SARS-CoV-2 genome suggest a role for cytosine deamination in CpG reduction. J Mol Cell Biol 13:225–227. https://doi.org/10.1093/jmcb/mjab011

Samuel CE (2012) ADARs, viruses and innate immunity. Curr Top Microbiol Immunol 37:435. https://doi.org/10.1007/82_2011_148

Simmonds P, Azim Ansari M (2021) Extensive C->U transition biases in the genomes of a wide range of mammalian RNA viruses; potential associations with transcriptional mutations, damage- or host-mediated editing of viral RNA. PLoS Pathog 17:1–25. https://doi.org/10.1371/journal.ppat.1009596

Simmonds P (2020) Rampant C→U hypermutation in the genomes of SARS-CoV-2 and other coronaviruses: causes and consequences for their short- and long-term evolutionary trajectories. mSphere 5:1–13. https://doi.org/10.1128/msphere.00408-20

Smith EC, Blanc H, Vignuzzi M, Denison MR (2013) Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. PLoS Pathog 9. https://doi.org/10.1371/journal.ppat.1003565

Song Y, He X, Yang W, et al (2021) ADAR mediated A-to-I RNA editing affects SARS-CoV-2 characteristics and fuels its evolution. bioRxiv 2021.07.22.453345

Sowden M, Hamm JK, Spinelli S, Smith HC (1996) Determinants involved in regulating the proportion of edited apolipoprotein B RNAs. RNA 2:274–288

Suspene R, Aynaud M-M, Koch S et al (2011) Genetic editing of herpes simplex virus 1 and Epstein-Barr herpesvirus genomes by human APOBEC3 cytidine deaminases in culture and in vivo. J Virol 85:7594–7602. https://doi.org/10.1128/jvi.00290-11

Tasakis RN, Samaras G, Jamison A, et al (2021) SARS-CoV-2 variant evolution in the United States: high accumulation of viral mutations over time likely through serial Founder Events and mutational bursts. PLoS One 16. https://doi.org/10.1371/journal.pone.0255169

Taylor DR, Puig M, Darnell MER et al (2005) New antiviral pathway that mediates hepatitis C virus replicon interferon sensitivity through ADAR1. J Virol 79:6291–6298. https://doi.org/10.1128/jvi.79.10.6291-6298.2005

Tomaselli S, Galeano F, Locatelli F, Gallo A (2015) Adars and the balance game between virus infection and innate immune cell response. Curr Issues Mol Biol 17:37–52. https://doi.org/10.21775/cimb.017.037

Tonkin-Hill G, Martincorena I, Amato R et al (2021) Patterns of within-host genetic diversity in SARS-COV-2. Elife 10:1–25. https://doi.org/10.7554/eLife.66857

van Dorp L, Richard D, Tan CCS, et al (2020) No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2. Nat Commun 11. https://doi.org/10.1038/s41467-020-19818-2

Vartanian JP, Meyerhans A, Asjö B, Wain-Hobson S (1991) Selection, recombination, and G—A hypermutation of human immunodeficiency virus type 1 genomes. J Virol 65:1779–1788. https://doi.org/10.1128/jvi.65.4.1779-1788.1991

Vartanian J (2008) Evidence for editing of human papillomavirus DNA by APOBEC3 in benign and precancerous lesions. Science (80-) 230:230–233. https://doi.org/10.1126/science.1153201

Voloch CM, Da Silva FR, De Almeida LGP et al (2021) Intra-host evolution during SARS-CoV-2 prolonged infection. Virus Evol 7:1–11. https://doi.org/10.1093/ve/veab078

Wang Y, Wang D, Zhang L et al (2021) Intra-host variation and evolutionary dynamics of SARS-CoV-2 populations in COVID-19 patients. Genome Med 13:1–13. https://doi.org/10.1186/s13073-021-00847-5

Yang Y, Sowden MP, Yang Y, Smith HC (2001) Intracellular trafficking determinants in APOBEC-1, the catalytic subunit for

cytidine to uridine editing of apolipoprotein B mRNA. Exp Cell Res 267:153–164. https://doi.org/10.1006/excr.2001.5255

Yang W, Wang Q, Howell KL et al (2005) ADAR1 RNA deaminase limits short interfering RNA efficacy in mammalian cells. J Biol Chem 280:3946–3953. https://doi.org/10.1074/jbc.M407876200

Zahn RC, Schelp I, Utermöhlen O, von Laer D (2007) A-to-G hypermutation in the genome of lymphocytic choriomeningitis virus. J Virol 81:457–464. https://doi.org/10.1128/jvi.00067-06

Zong J, Zhang Y, Guo F, et al (2022) Poor evidence for host-dependent regular RNA editing in the transcriptome of SARS- -CoV-2. J Appl Genet