THE MIND Bulletin on Mind-Body Medicine Research

Mind-Body Medicine Research Council

*Commentary*

# Viruses May Be Redefined as Self-Replicating Entities: Expanding the Definition of Life

by George B. Stefano[1*], Pascal Büttiker[1], Simon Weissenberger[2], Martin Anders[1], Jiri Raboch[1], Richard M. Kream[1]

[1] Department of Psychiatry, First Faculty of Medicine, Charles University and General University Hospital in Prague, Ke Karlovu 11, 120 00 Prague, Czech Republic

[2] Department of Psychology, University of New York in Prague, Prague, Czech Republic

*Correspondence: gstefano@sunynri.org

doi: 10.61936/themind/202412122

Viruses have traditionally been classified as non-living because they require a host cell for replication (reviewed in (Harris & Hill, 2020; Stefano & Kream, 2022b). However, extensive research has greatly advanced our understanding of how viruses hijack and manipulate host regulatory and metabolic processes to produce infectious progeny. The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has prompted a reconsideration of viruses as potentially living entities (Harris & Hill, 2020; Stefano & Kream, 2022b). SARS-CoV-2 comprehensively controls cellular processes; this suggests that its linear single-stranded (ss)RNA genome encodes a dynamic informational system that is capable of responding to evolutionary constraints (G. Stefano et al., 2023).

While some individuals can host viruses with no noticeable effects, the same virus may trigger an immune and neural responses in others (Zheng & Savitz, 2023; Zheng et al., 2023). We speculate that this variability is based largely on the virus' molecular structure, which can take on different conformations to adapt to a target molecule. These conformations may align well with the host's molecular system and thus result in no or few specific effects; others may induce harmful outcomes. A virus frequently interacts partially with a host and may not influence an entire molecular pathway (G. Stefano et al., 2023; Zheng et al., 2023). This limitation might explain why a virus might only be able to take over a host system when it finds the compatible "fit" needed to achieve the desired outcome, e.g., reproduction. This process must proceed rapidly and target the genetic processes of the host that are involved in reproduction and energy metabolism (e.g., mitochondria) in order to escape a defensive immune response (Trubetskoy et al., 2022), most notably early in the infection process, thereby facilitating viral targeting and immune neutralization. Additionally, the microenvironment, including thermodynamic influences, may also elicit conformational changes in the virus, thereby facilitating dynamic communication between molecules involved (Bitra et al., 2019; Stefano & Kream, 2022b).

The evolutionary constraints that favor viral host hijacking have shaped the ssRNA genome of SARS-CoV-2 into a three-dimensional structure defined by conserved base-pairing and complex secondary and tertiary configurations (Stefano & Kream, 2022b). Regulatory control of the virus's infectious processes relies heavily on extensive protein-protein interactions that direct conformational matching and shape recognition of viral and host nucleic acids and

proteins. The seamless integration of complex replicative processes depends on the precise nature of the complementary nucleotide sequences and their corresponding structural and non-structural viral proteins. Interestingly, the virus's ability to commandeer transcriptional and translational activities within specific cellular domains resembles artificial intelligence strategies, as both are fluid, self-correcting, and adaptive to change (Stefano & Kream, 2022b; Stefano et al., 2024).

Moreover, both intracellular bacterial pathogens and mitochondria, which originated from ancient bacterial species can reproduce in a eukaryotic cell; a virus pathogen is thus not unique in this regard (McClure et al., 2017; Murphy & O'Neill, 2024). Multifaceted mitochondrial disorders have also been associated with human disease (Angrand et al., 2021; Marques et al., 2024). Thus, we sought to examine the sequences of introns, which are currently emerging as biologically important reservoirs of genetic information similar to what has been described for mitochondrial heteroplasmy (Stefano & Kream, 2022a; Stewart & Chinnery, 2015). Though introns do not encode amino acid sequences, they play several critical roles in gene expression and its regulation (Birkholz et al., 2024; Girardini et al., 2023; LaRoche-Johnston et al., 2018; LaRoche-Johnston et al., 2023; Shaul, 2017). As a group, these reports highlight the functional significance of introns based on several of their important properties. Among these, introns contain regulatory elements, including enhancers and silencers, that control the timing, location, and level of gene expression. Introns also facilitate alternative splicing of mRNA and allow different combinations of exons to produce multiple protein variants from a single gene. Overall, this serves to increase protein diversity and facilitate complex regulation of cellular functions. Furthermore, intron splicing is essential for the proper export of mRNA from the nucleus to the cytoplasm, where translation into proteins occurs. Some introns have an impact on mRNA stability and lifespan, thereby altering its availability for translation. Introns also provide evolutionary flexibility by acting as buffers against mutations and allowing new gene functions to evolve without disrupting original protein function. Finally, introns contribute to the genomic organization and have a significant impact on the architecture and accessibility of chromatin (Birkholz et al., 2024; Girardini et al., 2023; LaRoche-Johnston et al., 2018; LaRoche-Johnston et al., 2023; Shaul, 2017).

Introns can be influenced by intracellular pathogens through a variety of mechanisms, including viral integration and excision, which disrupts normal splicing; viral manipulation of splicing machinery to favor its own protein production; horizontal bacterial gene transfer, which facilitates the introduction of new genetic material into introns; modulation of the host's immune response by altering pre-mRNA splicing; bacteria-mediated introduction of insertion sequences or transposons, thereby disrupting splicing; and infection-induced epigenetic changes, such as DNA methylation or histone modification that also affect gene expression and splicing (Birkholz et al., 2024; Birkholz et al., 2023; Kurosawa et al., 2023; LaRoche-Johnston et al., 2018; LaRoche-Johnston et al., 2023). These interactions have a significant impact on host gene expression and cellular function, contribute to the pathogenesis of infection, and promote the evolution of host-pathogen interactions.

An examination of the presence and influence of introns may substantiate the concept of life as a simple process of self-replication. Intronic variants that lead to splice alterations have been identified as the underlying factors contributing to dystrophinopathy, neurofibromatosis type I, and inherited retinal diseases (Koczkowska et al., 2023; Kurosawa et al., 2023; Waldrop et al., 2022). These splice-altering variants lead to the formation of pathogenic pseudoexons and the extension of existing exons via disruption of the recognition process via the actions of splicing factors such as small nuclear ribonucleoproteins and RNA-binding proteins. These splicing alterations result in mRNA destabilization through nonsense-mediated decay or result in functional defects in the encoded proteins (Koczkowska et al., 2023; Kurosawa et al., 2023; Waldrop et al., 2022).

Group II introns are ancient genetic elements that have greatly influenced the development of

modern eukaryotic genomes. These are self-splicing ribozymes that share a common ancestor with telomerase, the spliceosome, and many spliceosomal introns and non-long terminal repeat retroelements (LaRoche-Johnston et al., 2018). As a result, over half of the human genome includes elements that are derived from ancient group II introns which play crucial roles in promoting genetic function and diversity. Similarly, group II intron-related elements in bacteria, for example, abortive phage infection retroelements, diversity-generating retroelements, and some CRISPR-Cas systems have evolved to provide significant benefits to their hosts (LaRoche-Johnston et al., 2018).

By contrast, bacterial group II introns are rare, unevenly distributed, and often spread by lateral transfer. Thus, these are viewed mainly as "selfish" genetic elements that provide no benefits to the host (LaRoche-Johnston et al., 2018). However, new research has discovered that these introns can generate genetic diversity in bacteria at the RNA level (LaRoche-Johnston et al., 2018). The results of this study revealed that the Lactococcus lactis Ll.LtrB intron can recognize and insert itself into specific sequences in cellular mRNAs by reverse splicing. This insertion and subsequent circularization collectively induce a novel trans-splicing pathway that creates chimeric RNA molecules. This finding identified new splicing mechanisms in bacteria that, similar to the spliceosome in eukaryotes, increase RNA-level genetic diversity and highlight further connections between group II introns, spliceosomal introns, and the spliceosome (LaRoche-Johnston et al., 2018).

Homing endonucleases, which can facilitate interference, are widely distributed across diverse families of phages, fungi, and archaea (Birkholz et al., 2023). A small subset of these endonucleases that are highly conserved with human glycoprotein gp210 can be found in jumbo phages that infect a wide variety of host cells, including both Gram-negative and Gram-positive bacterial species. Additionally, every mobile intron has the potential to evolve into a weapon given the differences in divergence rates observed between conserved target sites and the surrounding genome. This mechanism is particularly significant when considering the evolution of viruses, which are constantly competing with one another through co-infection and have rapid replication rates that allow even a small selective advantage to be amplified quickly (Birkholz et al., 2023). More broadly, a greater understanding of the fitness advantages provided by weaponized mobile introns could be relevant to any intracellular genetic competition, including those between plasmids, viruses, and their hosts, under the right circumstances.

Specifically, a viruses' ability to infect the brain, as an example of their infectivity, is relevant to their potential to cause neuroinflammation and neurodegeneration. Several viruses, including herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV), can enter brain tissue and lead to conditions like encephalitis, neurocognitive disorders, and long-term brain damage (see (Buttiker et al., 2022; de Almeida, 2021; Li et al., 2015; Limongi & Baldelli, 2016; Meyding-Lamadé et al., 2019; Tomonaga, 2004; Wongchitrat et al., 2024)). HSV-1 and VZV can reactivate and cause lasting harm, while CMV and HIV are particularly dangerous for immunocompromised individuals. Other viruses, such as rabies, West Nile, Zika, and Epstein-Barr virus (EBV), are linked to both acute and chronic neurological impairments, with some, like EBV, implicated in multiple sclerosis (see (Buttiker et al., 2022; de Almeida, 2021; Li et al., 2015; Limongi & Baldelli, 2016; Meyding-Lamadé et al., 2019; Tomonaga, 2004; Wongchitrat et al., 2024)). In this regard, viral targeting of bacteria, which includes mitochondria given their long evolutionary interaction/relationship, probably is the basis for targeting energy metabolism (Stefano et al., 2024). Research is ongoing into the role of viral infections in neurodegenerative diseases, including Alzheimer's and Parkinson's.

Furthermore, considering the novel concept that viruses are alive adds to their sphere of influence, including potential novel treatment modalities. Thus, their metabolic pathways, cellular machinery, and autonomous growth

could be directly targeted by drugs, making it easier to disrupt their replication and survival. Additionally, their more complex structures would improve immune system recognition, enhancing vaccine effectiveness. Living viruses would also depend on specific environmental conditions, which may be manipulated to control infections. While they might develop resistance mechanisms, these could also be targeted, ultimately making viruses more vulnerable to various treatments, for example, limiting neurodegenerative actions.

Importantly, mitochondria organelles within eukaryotic cells are not classified as independent living entities, as they cannot survive outside the cell (Cutler, 1978; Malina et al., 2018). However, their unique features, such as possessing their own DNA, replicating through binary fission, and their critical role in cellular energy production reflect their evolutionary origins as once free-living prokaryotes. Notably, recent studies have demonstrated that mitochondria can function and exist in extracellular spaces ( see(G. B. Stefano et al., 2023; Zhou et al., 2024)). Furthermore, their genetic material can integrate into eukaryotic DNA, in a manner somewhat reminiscent of viral behavior (Wei et al., 2022). Additionally, the first pathogenic inversion in human mtDNA was documented by Musumeci et al., (Musumeci et al., 2000). More recently, Chanin and colleagues highlighted phase variation in bacteria, which is a mechanism enabling rapid genomic changes that enhance adaptability and survival (Chanin et al., 2024). This process, where recombinases flip a genomic region enhancing messaging, is notable because it occurs in bacteria, underscoring mitochondrial functionality as a conserved evolutionary mechanism, potentially unmasking their alive status. This mechanism supports survival through quick adaptation, influenced by microenvironmental factors. Thus, similar to viruses, mitochondria exhibit processes associated with self-replication, which raises questions about whether they too might warrant classification as living entities.

In summary, we propose that, contrary to conventional thinking, viruses are either alive or can become alive when found in an appropriate compatible environment, such as a eukaryotic cell. As with mitochondria, several characteristics of viruses support this conclusion: they can communicate with both prokaryotic and eukaryotic cells due to their shared chemical composition (e.g., nucleic acids), reproduce themselves, alter cellular energy metabolism to enhance their reproductive processes, survive and thrive in life-sustaining environments, and have optimized their replication process by adapting to host mechanisms that match their specific requirements, exhibiting molecular identity and diversity for the past two billion years. We speculate that during the course of evolution, early viral prototypes, similar to environmental DNA (Yang et al., 2022), eventually acquired the ability to self-replicate within a suitable coacervate-like droplet stage in environment (Agrawal et al., 2022; van Swaay et al., 2015), thus emerging as living entities. Additionally, achieving living status was facilitated by the virus's capacity for spontaneous, high-frequency mutations, surpassing those of prokaryotes and eukaryotes. This significantly higher mutation rate likely enabled the development of a streamlined genetic code, allowing these entities to adapt to a wide range of compatible hosts. Therefore, an improved understanding of the self-supporting and self-reproducing behavior of viruses could open new pathways for biomedical research, e. g., neurodegeneration, that encompass both pathological and beneficial potential.

**Acknowledgements:** Pascal Büttiker is currently a Ph D candidate and awarded a stipend in the Department of Psychiatry, First Faculty of Medicine, Charles University and General University Hospital Prague, Czech Republic. In part, it is acknowledged this document contains key elements that GBS presented as keynote speaker at the International Scientific Conference of Mind-Body Medicine (Nov. 4. 2024, Witten, Germany). During the preparation of this document, Dr Radek Ptacek passed away. We honor his memory with this document.

**Conflict of Interest:** The authors declare that they have no competing interests.

**Funding:** This work, in part, was supported by Cooperation Program, research area Neuroscience, and by the project MH CZ – DRO VFN64165.

***References***

Agrawal, A., Douglas, J. F., Tirrell, M., & Karim, A. (2022). Manipulation of coacervate droplets with an electric field. *Proc Natl Acad Sci U S A*, *119*(32), e2203483119. https://doi.org/10.1073/pnas.2203483119

Angrand, L., Boukouaci, W., Lajnef, M., Richard, J. R., Andreazza, A., Wu, C. L., Bouassida, J., Rafik, I., Foiselle, M., Mezouad, E., Naamoune, S., Chami, L., Mihoub, O., Salah, S., Benchaaben, A., Le Corvoisier, P., Barau, C., Costes, B., Yolken, R., . . . Tamouza, R. (2021). Low peripheral mitochondrial DNA copy number during manic episodes of bipolar disorders is associated with disease severity and inflammation. *Brain Behav Immun*, *98*, 349-356. https://doi.org/10.1016/j.bbi.2021.09.003

Birkholz, E. A., Morgan, C. J., Laughlin, T. G., Lau, R. K., Prichard, A., Rangarajan, S., Meza, G. N., Lee, J., Armbruster, E., Suslov, S., Pogliano, K., Meyer, J. R., Villa, E., Corbett, K. D., & Pogliano, J. (2024). An intron endonuclease facilitates interference competition between coinfecting viruses. *Science*, *385*(6704), 105-112. https://doi.org/10.1126/science.adl1356

Birkholz, E. A., Morgan, C. J., Laughlin, T. G., Lau, R. K., Prichard, A., Rangarajan, S., Meza, G. N., Lee, J., Armbruster, E. G., Suslov, S., Pogliano, K., Meyer, J. R., Villa, E., Corbett, K. D., & Pogliano, J. (2023). A mobile intron facilitates interference competition between co-infecting viruses. *bioRxiv*. https://doi.org/10.1101/2023.09.30.560319

Bitra, A., Nemcovicova, I., Picarda, G., Doukov, T., Wang, J., Benedict, C. A., & Zajonc, D. M. (2019). Structure of human cytomegalovirus UL144, an HVEM orthologue, bound to the B and T cell lymphocyte attenuator. *J Biol Chem*, *294*(27), 10519-10529. https://doi.org/10.1074/jbc.RA119.009199

Buttiker, P., Stefano, G. B., Weissenberger, S., Ptacek, R., Anders, M., Raboch, J., & Kream, R. M. (2022). HIV, HSV, SARS-CoV-2 and Ebola Share Long-Term Neuropsychiatric Sequelae. *Neuropsychiatr Dis Treat*, *18*, 2229-2237. https://doi.org/10.2147/NDT.S382308

Chanin, R. B., West, P. T., Wirbel, J., Gill, M. O., Green, G. Z. M., Park, R. M., Enright, N., Miklos, A. M., Hickey, A. S., Brooks, E. F., Lum, K. K., Cristea, I. M., & Bhatt, A. S. (2024). Intragenic DNA inversions expand bacterial coding capacity. *Nature*. https://doi.org/10.1038/s41586-024-07970-4

Cutler, R. G. (1978). *Evolutionary Biology of Senescence* (J. A. Behnke, Finch, C.E., Moment, G.B., Ed.). Plenum Press.

de Almeida, S. (2021). Brain and Central Nervous System Infections: Viruses. In. https://doi.org/10.1016/B978-0-12-818731-9.00123-3

Girardini, K. N., Olthof, A. M., & Kanadia, R. N. (2023). Introns: the "dark matter" of the eukaryotic genome. *Front Genet*, *14*, 1150212. https://doi.org/10.3389/fgene.2023.1150212

Harris, H. M. B., & Hill, C. (2020). A Place for Viruses on the Tree of Life. *Front Microbiol*, *11*, 604048. https://doi.org/10.3389/fmicb.2020.604048

Koczkowska, M., Chen, Y., Xie, J., Callens, T., Gomes, A., Wimmer, K., & Messiaen, L. M. (2023). Analysis of 200 unrelated individuals with a constitutional NF1 deep intronic pathogenic variant reveals that variants flanking the alternatively spliced NF1 exon 31 [23a] cause a classical neurofibromatosis type 1 phenotype while altering

predominantly NF1 isoform type II. *Hum Genet*, *142*(7), 849-861. https://doi.org/10.1007/s00439-023-02555-z

Kurosawa, R., Iida, K., Ajiro, M., Awaya, T., Yamada, M., Kosaki, K., & Hagiwara, M. (2023). PDIVAS: Pathogenicity predictor for Deep-Intronic Variants causing Aberrant Splicing. *BMC Genomics*, *24*(1), 601. https://doi.org/10.1186/s12864-023-09645-2

LaRoche-Johnston, F., Monat, C., Coulombe, S., & Cousineau, B. (2018). Bacterial group II introns generate genetic diversity by circularization and trans-splicing from a population of intron-invaded mRNAs. *PLoS Genet*, *14*(11), e1007792. https://doi.org/10.1371/journal.pgen.1007792

LaRoche-Johnston, F., Prattico, C., Monat, C., Hinse, O., & Cousineau, B. (2023). First unraveling of the hidden and intricate evolutionary history of a bacterial group II intron family. *Evolution*, *77*(6), 1382-1395. https://doi.org/10.1093/evolut/qpad050

Li, W., Lee, M. H., Henderson, L., Tyagi, R., Bachani, M., Steiner, J., Campanac, E., Hoffman, D. A., von Geldern, G., Johnson, K., Maric, D., Morris, H. D., Lentz, M., Pak, K., Mammen, A., Ostrow, L., Rothstein, J., & Nath, A. (2015). Human endogenous retrovirus-K contributes to motor neuron disease. *Sci Transl Med*, *7*(307), 307ra153. https://doi.org/10.1126/scitranslmed.aac8201

Limongi, D., & Baldelli, S. (2016). Redox Imbalance and Viral Infections in Neurodegenerative Diseases. *Oxid Med Cell Longev*, *2016*, 6547248. https://doi.org/10.1155/2016/6547248

Malina, C., Larsson, C., & Nielsen, J. (2018). Yeast mitochondria: an overview of mitochondrial biology and the potential of mitochondrial systems biology. *FEMS Yeast Res*, *18*(5). https://doi.org/10.1093/femsyr/foy040

Marques, E., Kramer, R., & Ryan, D. G. (2024). Multifaceted mitochondria in innate immunity. *npj Metabolic Health and Disease*, *2*(1), 6. https://doi.org/10.1038/s44324-024-00008-3

McClure, E. E., Chavez, A. S. O., Shaw, D. K., Carlyon, J. A., Ganta, R. R., Noh, S. M., Wood, D. O., Bavoil, P. M., Brayton, K. A., Martinez, J. J., McBride, J. W., Valdivia, R. H., Munderloh, U. G., & Pedra, J. H. F. (2017). Engineering of obligate intracellular bacteria: progress, challenges and paradigms. *Nat Rev Microbiol*, *15*(9), 544-558. https://doi.org/10.1038/nrmicro.2017.59

Meyding-Lamadé, U., Craemer, E., & Schnitzler, P. (2019). Emerging and re-emerging viruses affecting the nervous system. *Neurological Research and Practice*, *1*(1), 20. https://doi.org/10.1186/s42466-019-0020-6

Murphy, M. P., & O'Neill, L. A. J. (2024). A break in mitochondrial endosymbiosis as a basis for inflammatory diseases. *Nature*, *626*(7998), 271-279. https://doi.org/10.1038/s41586-023-06866-z

Musumeci, O., Andreu, A. L., Shanske, S., Bresolin, N., Comi, G. P., Rothstein, R., Schon, E. A., & DiMauro, S. (2000). Intragenic inversion of mtDNA: a new type of pathogenic mutation in a patient with mitochondrial myopathy. *Am J Hum Genet*, *66*(6), 1900-1904. https://doi.org/10.1086/302927

Shaul, O. (2017). How introns enhance gene expression. *Int J Biochem Cell Biol*, *91*(Pt B), 145-155. https://doi.org/10.1016/j.biocel.2017.06.016

Stefano, G., Büttiker, P., Weissenberger, S., Esch, T., Anders, M., Raboch, J., Kream, R., & Ptacek, R. (2023). Independent and sensory human mitochondrial functions reflecting symbiotic evolution. *Frontiers in Cellular and Infection Microbiology*. https://doi.org/10.3389/fcimb.2023.1130197

Stefano, G. B., Buttiker, P., Weissenberger, S., Esch, T., Anders, M., Raboch, J., Kream, R. M., & Ptacek, R. (2023). Independent and sensory human mitochondrial functions reflecting symbiotic evolution. *Front Cell Infect Microbiol*, *13*, 1130197. https://doi.org/10.3389/fcimb.2023.1130197

Stefano, G. B., & Kream, R. M. (2022a). Mitochondrial DNA Heteroplasmy as an Informational Reservoir Dynamically Linked to Metabolic and Immunological Processes Associated with COVID-19 Neurological Disorders. *Cell Mol Neurobiol*, *42*(1), 99-107. https://doi.org/10.1007/s10571-021-01117-z

Stefano, G. B., & Kream, R. M. (2022b). Viruses Broaden the Definition of Life by Genomic Incorporation of Artificial Intelligence and Machine Learning Processes. *Curr Neuropharmacol*, *20*, 1888-1893. https://doi.org/10.2174/1570159X20666220420121746

Stefano, G. B., Weissenberger, S., Ptacek, R., Anders, M., Raboch, J., & Buttiker, P. (2024). Viruses and Mitochondrial Dysfunction in Neurodegeneration and Cognition: An Evolutionary Perspective. *Cell Mol Neurobiol*, *44*(1), 68. https://doi.org/10.1007/s10571-024-01503-3

Stewart, J. B., & Chinnery, P. F. (2015). The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. *Nat Rev Genet*, *16*(9), 530-542. https://doi.org/10.1038/nrg3966

Tomonaga, K. (2004). Virus-induced neurobehavioral disorders: mechanisms and implications. *Trends Mol Med*, *10*(2), 71-77. https://doi.org/10.1016/j.molmed.2003.12.001

Trubetskoy, V., Pardinas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., Chen, C. Y., Dennison, C. A., Hall, L. S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J. C., Koopmans, F., Magnusson, S., Richards, A. L., Sidorenko, J., . . . Schizophrenia Working Group of the Psychiatric Genomics, C. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *604*(7906), 502-508. https://doi.org/10.1038/s41586-022-04434-5

van Swaay, D., Tang, T. Y., Mann, S., & de Mello, A. (2015). Microfluidic Formation of Membrane-Free Aqueous Coacervate Droplets in Water. *Angew Chem Int Ed Engl*, *54*(29), 8398-8401. https://doi.org/10.1002/anie.201502886

Waldrop, M. A., Moore, S. A., Mathews, K. D., Darbro, B. W., Medne, L., Finkel, R., Connolly, A. M., Crawford, T. O., Drachman, D., Wein, N., Habib, A. A., Krzesniak-Swinarska, M. A., Zaidman, C. M., Collins, J. J., Jokela, M., Udd, B., Day, J. W., Ortiz-Guerrero, G., Statland, J., . . . Flanigan, K. M. (2022). Intron mutations and early transcription termination in Duchenne and Becker muscular dystrophy. *Hum Mutat*, *43*(4), 511-528. https://doi.org/10.1002/humu.24343

Wei, W., Schon, K. R., Elgar, G., Orioli, A., Tanguy, M., Giess, A., Tischkowitz, M., Caulfield, M. J., & Chinnery, P. F. (2022). Nuclear-embedded mitochondrial DNA sequences in 66,083 human genomes. *Nature*. https://doi.org/10.1038/s41586-022-05288-7

Wongchitrat, P., Chanmee, T., & Govitrapong, P. (2024). Molecular Mechanisms Associated with Neurodegeneration of Neurotropic Viral Infection. *Mol Neurobiol*, *61*(5), 2881-2903. https://doi.org/10.1007/s12035-023-03761-6

Yang, K., Wang, L., Cao, X., Gu, Z., Zhao, G., Ran, M., Yan, Y., Yan, J., Xu, L., Gao, C., & Yang, M. (2022). The Origin, Function, Distribution, Quantification, and Research Advances of Extracellular DNA. *Int J Mol Sci*, *23*(22). https://doi.org/10.3390/ijms232213690

Zheng, H., & Savitz, J. (2023). Effect of Cytomegalovirus Infection on the Central Nervous System: Implications for Psychiatric Disorders. *Curr Top Behav Neurosci*, *61*, 215-241. https://doi.org/10.1007/7854_2022_361

Zheng, H., Webster, M. J., Weickert, C. S., Beasley, C. L., Paulus, M. P., Yolken, R. H., & Savitz, J. (2023). Cytomegalovirus antibodies are associated with mood disorders, suicide, markers of neuroinflammation, and microglia activation in postmortem brain samples. *Mol Psychiatry*, *28*(12), 5282-5292. https://doi.org/10.1038/s41380-023-02162-4

Zhou, W., Karan, K. R., Gu, W., Klein, H. U., Sturm, G., De Jager, P. L., Bennett, D. A., Hirano, M., Picard, M., & Mills, R. E. (2024). Somatic nuclear mitochondrial DNA insertions are prevalent in the human brain and accumulate over time in fibroblasts. *PLoS Biol*, *22*(8), e3002723. https://doi.org/10.1371/journal.pbio.3002723