Journal of NeuroVirology (2026) 32:11
https://doi.org/10.1007/s13365-025-01303-5

RESEARCH

NeuroViOme: a viral orfeome collection for studies of neurodegenerative disease

Benjamin Weller[1] · Chung-Wen Lin[1] · Simin Rothballer[1] · Michael A. Calderwood[2,3,4] · Pascal Falter-Braun[1,5] · Claudia Falter[1]

Received: 8 November 2025 / Revised: 17 December 2025 / Accepted: 30 December 2025
© The Author(s) 2026

Abstract

Neurodegenerative diseases such as Alzheimer's and Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS) pose a global health challenge due to their progressive course and lack of curative therapies. These conditions lead to severe neurological decline, significantly impacting patient independence and quality of life, and ultimately result in lethal outcome. Emerging evidence suggests that viral infections contribute to the onset and progression of these neurological diseases, Leblanc and Vorberg (PLoS Pathog 18:e1010670, 2022), either by directly inducing neurological symptoms or by triggering immune responses resulting in neuropathology. Nevertheless, systematic studies of the direct interplay between viral and host proteins in neurodegeneration remain scarce. A key aspect of viral pathogenesis is direct interaction between viral and host proteins (protein–protein interactions, PPIs), which are essential for viral replication and can disrupt or redirect host cell function Kim et al. (Nat Biotechnol, 2022); Zhou et al. (Res Sq, 2022), potentially contributing to the development of diseases traditionally considered non-communicable. Understanding these molecular mechanisms is crucial for advancing diagnostic and therapeutic strategies in neurodegenerative conditions, particularly ALS and MS. To enable systematic studies of these interactions, we introduce *NeuroViOme* as ORFeome resource encompassing nearly all protein-coding sequences from nine viruses selected based on their prevalence, neurotropism, and mechanistic or epidemiological links to neurodegenerative processes. NeuroViOme includes ORFs from Enteroviruses (EV-A71, EV-D68, CVB3, Echovirus E30), Herpesviruses (HSV-1, EBV, HHV3/Varicella Zoster), the endogenous retrovirus HERV-K, and Polyomavirus JCPyV. To our knowledge, this represents the most comprehensive viral ORF set assembled for neurodegeneration research to date. The collection builds the foundation for interactome mapping and functional genomics analyses and provides a valuable basis for systematic studies of viral perturbations of host pathways.

Keywords Neurodegenerative diseases · Neurotrophic virus · Viral pathogenesis · ORFeome · Amyotrophic lateral sclerosis

✉ Benjamin Weller
benjamin.weller@helmholtz-munich.de

✉ Claudia Falter
claudia.falter@helmholtz-munich.de

[1] Institute of Network Biology (INET), Molecular Targets and Therapeutics Center, Helmholtz Center Munich, German Research Center for Environmental Health, Munich-Neuherberg, Germany

[2] Center for Cancer Systems Biology (CCSB), Dana-Farber Cancer Institute, Boston, MA, US

[3] Department of Genetics, Blavatnik Institute, Harvard Medical School, Boston, MA, US

[4] Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA, US

[5] Microbe-Host Interactions, Faculty of Biology, Ludwig-Maximilians-Universität (LMU) München, Planegg-Martinsried, Germany

Published online: 02 March 2026

Introduction

Increasing evidence suggests that viral infections can contribute to long-term conditions that extend beyond acute illness, including several neurodegenerative disorders (Levine et al. 2023). Although a direct causal relationship between viral exposure and diseases such as ALS has been examined for decades (Salazar-Grueso and Roos 1995), conventional attempts to detect persistent viral material in patient tissues have yielded limited success (Celeste and Miller 2018). Nonetheless, it is now widely recognized that viral insults can produce delayed or lasting neurological effects even after the primary infection has resolved (Carfi et al. 2020; Choutka et al. 2022; Greenhalgh et al. 2024), underscoring the need to better understand how viruses influence neurodegenerative processes.

Mechanistically, viruses may contribute to neurodegeneration because their replication depends on viral proteins that interact with, and modulate, host cellular pathways (Basic et al. 2014). Experimental studies have shown that even asymptomatic viral infections can interact with host genetic susceptibility to trigger chronic disease-like phenotypes (Cadwell et al. 2010). Virus–host protein–protein interactions (PPIs), while essential for viral propagation, can perturb neuronal homeostasis and reshape host interaction networks involved in neurodegenerative diseases (Wan et al. 2020). Previous systematic interactome studies from our group and others have demonstrated that mapping such molecular perturbations yields powerful mechanistic insights into how microbial and viral factors alter human cellular systems (Altmann et al. 2020; Calderwood et al. 2007; Gulbahce et al. 2012; Mukhtar et al. 2011; Wessling et al. 2014) (Kim et al. 2022; Osborne et al. 2023).

To enable similar approaches towards understanding viral contributions to neurodegenerative disorders we present the NeuroViOme, an open reading frame collection (ORFeome) for ORFs of nine viruses suspected to play a role in ALS, MS, AD and other neurodegenerative disorders.

Enabling systems-level analysis of viral drivers in neurodegeneration

Although ORFeome libraries are well established for many model organisms, comparable resources for viruses remain limited. Early initiatives showed that, despite the large number of sequenced viral genomes, only a small proportion of viral ORFs has been cloned in experimentally tractable formats, and usually only for individual pathogens, resulting in fragmented and heterogeneous collections (Pellet et al. 2010). Reviews in virus–host interactomics emphasize that, because comprehensive viral ORFeomes exist for only a few species, high-throughput studies typically rely on self-assembled, virus-specific ORF sets that are often incomplete or inconsistent across studies. Differences in cloning strategy, vector context, and annotation impact on experimental results (Braun et al. 2009; Varjosalo et al. 2013) and thus complicate integration of data across viruses and impede systematic comparisons of their host-targeting strategies, conserved mechanisms, or characteristic network perturbations (de Chassey et al. 2008; Pellet et al. 2010). Despite extensive progress in viral genome sequencing, only a fraction of viral coding sequences has been formatted for standardized functional assays, underscoring a persistent gap between available sequence information and experimentally accessible viral gene resources.

This gap is particularly important in neurodegeneration research, where viral exposure is increasingly recognized as a potential environmental contributor to disorders such as ALS, MS, Alzheimer's disease, or Parkinson's disease. Cohort studies and mechanistic analyses indicate that viral factors may act as biological "hits", which, according to the multiple-hits hypothesis (Patrick et al. 2019), interact with host genetic or immune susceptibilities to promote chronic neuroinflammation, protein aggregation or e.g. defective proteostasis towards neuronal dysfunction. Evaluating such mechanisms systematically often requires the ability to compare viral proteins across diverse viral families in a comprehensive manner, an undertaking that is now facilitated by the availability of a coherent viral ORF collection.

NeuroViOme directly addresses these challenges by providing an experimentally consistent platform for studying viral proteins from nine viruses spanning four viral families. By bringing these ORFs together in a single resource, cross-virus comparisons become feasible in ways that were previously limited by heterogeneous constructs and fragmented ORF availability. Importantly, ORF-based resources also lower the practical and biosafety barriers to virology, as isolated viral open reading frames can be examined without handling infectious virus. This greatly facilitates studies focused on the functions of individual viral proteins or their interactions with host factors, which can be performed without biosafety-level facilities and are therefore accessible to neurodegeneration laboratories that may not have specialized virological infrastructure. While ORFeome collections are not intended to model all aspects of viral infection, such as entry, replication, or immune evasion, they provide a powerful and complementary approach for dissecting protein-level mechanisms that contribute to host perturbation.

Within their intended scope, viral ORFeomes offer an accessible means to conduct reproducible and scalable functional assays, integrate viral perturbations into established disease models, and identify virus-specific or convergent pathways that may influence neuronal vulnerability.

Ultimately, such a resource expands the toolkit available for probing the molecular interface between viruses and neurodegenerative processes.

Evidence linking selected viral families to neurodegenerative processes

The NeuroViOme viral ORFeome comprises nine viruses selected for their documented or emerging relevance to neurodegenerative processes, their representation of diverse viral families, and their compatibility with systematic ORF-level functional studies. These viruses encompass high-prevalence pathogens with lifelong persistence, classically neurotropic agents causing CNS injury, and viruses associated with proteinopathy, neuroinflammation, or demyelinating pathology. This evidence-supported panel enables comparative analyses across heterogeneous viral mechanisms and provides a foundation for identifying convergent host pathways targeted by distinct viruses.

Herpesviruses constitute a central part of the collection due to their ubiquity, latency, and extensive neurological impact. Epstein–Barr virus (EBV) shows the strongest epidemiological link between a virus and a neurodegenerative condition: longitudinal cohort studies demonstrate that EBV seroconversion precedes multiple sclerosis (MS) onset and massively elevates MS risk (Bjornevik et al. 2022). Beyond MS, experimental work suggests that EBV may contribute to neurodegenerative conditions through mechanisms involving neuroinflammation, blood–brain barrier disruption, and viral activity within CNS-resident or infiltrating immune cells (Tiwari et al. 2022). Herpes simplex virus type 1 (HSV-1), another globally prevalent neurotropic virus, has been associated with Alzheimer's disease pathology, supported by evidence that HSV-1 infection promotes amyloid-β accumulation, tau phosphorylation, and microglial activation (De Chiara et al. 2010; Wozniak et al. 2007). Epidemiological interactions with APOE-ε4 further strengthen this link(Itzhaki et al. 1997). Beyond Alzheimer's disease, HSV-1 has also been reported to modulate neuroimmune and autophagy-related pathways, including optineurin, an autophagy receptor that restricts neuroinvasive HSV-1 infection and is implicated in ALS-related neurodegenerative mechanisms (Ames et al. 2021). Varicella–zoster virus (HHV3) has similarly been connected to neurodegenerative trajectories: reactivation induces neuroinflammation and can exacerbate pathology in the presence of latent HSV-1 (Cairns et al. 2022), while population-level studies report an elevated dementia risk following HHV3 infection (Blandi et al. 2025). Observational associations between shingles vaccination and reduced dementia incidence (Eyting et al. 2025) highlight the relevance of HHV3 as a potentially modifiable risk factor.

Enteroviruses add a distinct set of neurodegeneration-relevant mechanisms to the NeuroViOme panel. Enterovirus D68 (EV-D68) has been linked to acute flaccid myelitis and selective injury of anterior horn motor neurons, the same cellular population vulnerable in ALS and other motor neuron disorders, through combined viral, inflammatory, and protease-mediated mechanisms (Vogt et al. 2022). Enterovirus A71 (EV-A71) promotes neurodegeneration via astrocytic apoptosis (TLR7/IL-6 signaling) (Luo et al. 2019), motor neuron ferroptosis (Chooi et al. 2024), and TDP-43 cleavage (Wo et al. 2021). Coxsackievirus B3 (CVB3) contributes to neuropathology in both Parkinson's disease and ALS models by inducing α-synuclein(Park et al. 2021) and TDP-43 pathology (Xue et al. 2022), impairing proteostasis, and accelerating disease progression in genetically susceptible mice. Echovirus 30 (E30), a leading cause of aseptic meningitis and encephalitis, shows neuroinvasive capacity and elicits chronic inflammatory and synaptic gene-expression changes that overlap with pathways implicated in neurodegeneration(Li et al. 2022).

The neurovirulent polyomavirus JCPyV adds a distinct glial component to the panel. Beyond its established role in progressive multifocal leukoencephalopathy, transcriptomic analyses reveal extensive immune activation, blood–brain barrier disruption, and potential neuronal involvement even outside classical immunosuppressed contexts (Honkimaa et al. 2024).

Finally, HERV-K, an endogenous retrovirus belonging to the human endogenous retroviral repertoire that comprises about 8% of the genome, was included based on evidence that its reactivation is associated with autoimmune diseases, cancers, and neurological disorders (Garcia-Montojo et al. 2024), and that its envelope protein contributes to neurotoxicity and TDP-43 pathology in ALS(Steiner et al. 2022).

Viruses were further evaluated for feasibility and completeness of ORF annotation to ensure compatibility with our sequence-verified Gateway cloning pipeline. HTLV-1, despite neurological relevance, could not be incorporated because its ORFs are absent from the human ORFeome collection, while HIV-1 was excluded due to its distinct research landscape and availability of existing dedicated ORFeomes. The resulting set captures major neurotropic, neuroinflammatory, and neurodegenerative mechanisms while enabling systematic, cross-virus analyses that can reveal shared host targets and convergent pathogenic pathways. Comprehensive analyses of the virus–host interactome derived from this resource, including extensive functional validation, are currently ongoing and will be reported in a dedicated manuscript upon completion.

Key clinical and mechanistic features, along with a qualitative evidence level for neurodegenerative involvement, are compiled for all included viruses (see Table 1).

Table 1 Neurological relevance of viruses included in the NeuroViOme ORFeome – summary

Virus	Viral Group	Main clinical manifestations	Neurotropism (main)	Key neurodegenerative mechanisms (examples)	Level of evidence*
EBV	Herpesviridae	Infectious mononucleosis	CNS	Epidemiological link to MS; evidence for AD-related Aβ and tau changes; immune-mediated neurodegeneration	**Strong**
HSV-1	Herpesviridae	Oral herpes, encephalitis	Trigeminal ganglia, latent	Promotes Aβ accumulation, tau phosphory-lation, neuroinflam-mation; AD, MS, ALS association	**Strong**
HHV3 (Varicello-virus)	Herpesviridae	Varicella, shingles	Peripheral ganglia, latent	Reactivation triggers neuroin-flammation, may induce HSV 1 reactivation and AD like patho-logy; epidemiological links to dementia	**Moderate**
EV-D68	Enterovirus D	Respiratory disease, acute flaccid myelitis (AFM)	Motor neurons in ante-rior horn of spinal cord	Motor neuron infection, inflammation, disruption of nucleocyto-plasmic transport; relevance to motor neuron disease mechan.	**Emerging**
EV-A71	Enterovirus A	hand, foot, and mouth disease (HFMD)	Astrocytes, motor neurons	TLR7/IL-6–mediated astrocytic apopto-sis, ferroptosis in motor neurons, TDP-43 cleavage	**Moderate–Emerging**
CVB3	Enterovirus B	Myocarditis, meningitis	CNS	Induction of α-syn aggregates, TDP-43 mislocalization, exacerbation of ALS-like pathology in susceptible models	**Moderate**
E30	Enterovirus B	HFMD, AFM, asep-tic meningitis	CNS, neurons, glia	Chronic inflammation, impaired neurogen-esis, synaptic gene dysregulation; mechanistic overlap with neurodegenerative pathways	**Emerging**
HERV-K	Human endogenous retrovirus	Endogenous, reacti-vated in disease	Neurons, neural stem cells	TDP-43 proteinopathy, direct neurotoxicity of env, ALS-like degeneration in transgenic models	**Strong**
JCPyV	Polyomaviridae	PML	Oligodendrocytes glia, CNS	Demyelination, neuroinflammation, BBB disruption	**Strong**

*Evidence level integrates epidemiology, neurotropism, and mechanistic data

Methods

Viral protein-coding ORFs were obtained from several sources or generated in Entry vectors for compatibility with the Gateway cloning system(Walhout et al. 2000). This recombinational cloning system enables the highly efficient transfer of ORFs into identical expression plasmids and is therefore uniquely suited for standardized functional assays (Altmann et al. 2018; Walhout et al. 2000). A comprehensive collection of HSV-1 ORFs in pENTR207 (NovoPro Bioscience Inc. Cat.#: V011826) or pENTR221 (Thermo Fisher Cat.#: 12536017) were acquired from the DNASU Plasmid Repository(Rolfs et al. 2008; Seiler et al. 2014; Yu et al. 2014). An EBV ORF collection in pENTR223 (NovoPro Bioscience Inc. Cat.#: V011817) was obtained from the Center for Cancer Systems Biology (CCSB) at the Dana-Farber Cancer Institute(Calderwood et al. 2007). All remaining ORFs were generated by gene synthesis. To ensure a coherent and reproducible ORFeome suitable for systematic functional studies, we defined explicit criteria for ORF identification. Reference genome sequences and their annotations were downloaded from the NCBI database to identify protein-coding ORFs for *Varicella Zoster Virus* (HHV3: NC_001348.1), *Polyomavirus* (JCPyV: NC_001699.1), HERV-K (HERV-K113: NC_022518.1), *Enterovirus 71* (EV-A71: MG208882.1), *Enterovirus D68* (EV-D68: NC_038308.1), *Echovirus 30* (E30: ON129560.1), *Coxsackievirus B3* (EV-B3: U57056.1) and *Epstein-Barr virus* (EBV: NC_007605.1). ORFs were derived from the respective NCBI reference genome annotation and each coding sequence was evaluated for uniqueness determined at the protein-sequence level. ORFs encoding identical amino-acid sequences were represented once, whereas annotated internal ORFs were treated as separate entities. Proteolytic cleavage products of polyproteins derived from one transcript were also treated as separate entities (ORFs), when annotated in the respective reference genome. Partial constructs covering specific protein domains were incorporated only when they were present in existing validated libraries (e.g., DNASU HSV-1). These constructs were not counted as independent ORFs but were retained as optional tools for domain-specific analyses. For genes subject to long-range alternative splicing, specifically from herpesvirus genomes, in line with established approaches for ORFeome collections for, e.g., the human ORFeome (Luck et al. 2020), the longest mRNA structure as represented in the respective reference genome was chosen in order to ensure consistency and comparability across viruses.

Sequences for EBV ORFs obtained from CCSB were aligned to the respective coding sequences from the reference genome. Of the 87 ORFs in the reference genome, 7 differed in sequence and 4 were missing from the CCSB collection.

Therefore 10 of these 11 ORFs were included for gene synthesis. The ORFs for EBV protein BPLF1 and gp24 of HHV3 could not be synthesized due to their sizes of >9 kb and >8 kb, respectively. In addition, the HHV3 reference genome contains three ORF pairs with identical sequences.

In total, 122 viral ORF sequences were compiled for gene synthesis. For all sequences, a translational start codon was added, if not present in the native sequence. Two nucleotides (gc) were added in front of the translational start codon for in-frame fusion to N-terminal tags in Gateway expression plasmids upon LR recombination reaction. Stop codons were removed, where present, and replaced with a unified stop codon, TAA, to facilitate its potential removal by PCR with a universal primer for applications requiring C-terminal fusion constructs. Sequences were then uploaded to the gene synthesis web interface from Twist Bioscience (San Francisco, CA, USA) for evaluation. Eight sequences were not accepted for synthesis due to long direct repeats, small repeats, areas with high GC content or a combination thereof. These sequences were codon optimized for *S. cerevisiae*, producing synthesizable sequences for seven of these ORFs. From the four Enteroviruses, gene synthesis for the respective proteolytic cleavage product ORF 3B was not possible due to high repeat density in the corresponding annotated nucleotide sequences, even after codon optimization. For these small ORFs of 66 nucleotides, each ORF was placed in three tandem repeats, separated by a glycine linker (ggtggc), followed by codon optimization, yielding synthesizable sequences. Finally, the reference sequence for ORF 3 C from the polyprotein of EV-A71 contained degenerate base code at three positions. This sequence was aligned to GenBank accession LC626894.1 (*Enterovirus A71* 2488-Yamagata-2006 RNA) to replace the degenerate code with the respective nucleotides at those positions.

ORF sequences > 300 nucleotides were generated as clonal genes in pTwistENTR (Twist Biosciences) and NGS-verified at Twist Bioscience (n = 117). For sequences < 300 nucleotides, Gateway recombination sites were added to the 5'-end (attB1: GGGGACAAGTTTGTACAAAAAAGCAGGCT) and 3'-end (attB2: ACCCAGCTTTCTTGTACAAAGTGGTCCCC) and subsequently synthesized as gene fragments ($n = 16$). The obtained fragments were cloned into pDONR223 by BP recombination reaction. The resulting Entry clones were isolated from single colonies and verified by Sanger sequencing.

Results

The NeuroViOme ORFeome as Gateway Entry clone collection, represents, to our knowledge, the most comprehensive viral ORF collection associated with neurodegenerative disease risk assembled to date. Covering almost 90% of the protein-coding capacity of nine neurodegeneration-associated viruses, this resource provides an important foundation for systematic studies of viral contributions to human neurological disorders. The breadth of the collection, containing the genomes of the *Enteroviruses EV-A71*, EV-D68, CVB3 and *Echovirus E30*, the human endogenous retrovirus HERVK, the Herpesviruses HSV-1, EBV and HHV3/Varicella Zoster, and the *Polyomavirus JCPyV* (s. Table 2) enables parallel interrogation of conserved and virus-specific mechanisms across distinct viral families, spanning positive-sense RNA viruses, herpesviruses, retroviruses, and polyomaviruses.

In total, the NeuroViOme ORFeome contains 247 of the 285 unique ORFs within the reference genomes from the nine viruses as full-length Entry clones. The clones were compiled from several sources. HSV-1 ORFs were acquired from the DNASU plasmid repository, covering 59 of 74 ORFs from the HSV-1 reference genome (accession #: X14112.1) as full-length clones. Six additional ORFs are only covered as partial sequences encoding N- or C-terminal fragments of the viral protein, respectively. Such partial sequences also exist for 15 further ORFs that are also available as full-length constructs. Moreover, many constructs are available as open (lacking a stop codon) and closed (with stop codon) forms.

Table 2 NeuroViOme coverage and Composition - Summary

Virus	Accession #	# of unique ORFs in ref. seq.	# of unique, full-length ORFs in NeuroViOme	Coverage	Total # of ORFs in NeuroViOme	Source
EBV	NC_007605.1	87	75	86%	80	CCSB/gene synthesis
HSV-1	X14112.1	74	59	80%	181	DNASU
HHV3	NC_001348.1	70	63	90%	63	Gene synthesis
EV-D68	NC_038308.1	11	10	91%	10	Gene synthesis
EV-A71	MG208882.1	11	10	91%	10	Gene synthesis
EV-B3 (CVB3)	U57056.1	11	10	91%	10	Gene synthesis
EV30 (E30)	ON129560.1	11	10	91%	10	Gene synthesis
HERV-K	NC_022518.1	4	4	100%	4	Gene synthesis
JCPyV	NC_001699.1	6	6	100%	6	Gene synthesis
Total		285	247	87%	374	

Of the 87 ORFs in the EBV reference genome, 75 are included in the ORFeome collection. Analysis of sequences from 92 putative full length EBV ORFs provided by the CCSB revealed that six had between 9 and 312 additional nucleotides at the 5'-end compared to the respective reference sequences. Additionally, four EBV reference ORFs were not present as full-length clones. These ORFs were generated by gene synthesis to supplement the EBV part of the ORFeome (see materials and methods). By further analysis of CCSB-derived clones by PCR evaluation of insert size, as well as Sanger sequencing, the full-length sequences for 11 ORFs could not be confirmed and were therefore removed from the collection.

The reference genome of HHV3 contains 70 unique ORF sequences, of which 63 are represented in the NeuroViOme collection. The genome structure of the four Enteroviruses EV-A71, EV30, EV-D68 and CVB3 are identical, each consisting of 11 ORFs following the same gene nomenclature. Except for the four ORF2As ORFs, which could not be cloned possibly due to toxicity of the encoded protease, all remaining 40 ORFs of the Enteroviruses are included in NeuroViOme. Finally, all six ORFs from the polyomavirus JCPyV, as well as the four coding sequence elements of the human endogenous retrovirus HERV-K113 are included in this collection. The constructs for these seven viruses were generated by gene synthesis and analyzed via NGS or Sanger sequencing (see materials and methods).

In total and including partial coding sequences for six HSV-1 ORFs (UL27, UL28, UL37, UL46, UL56 and UL9), NeuroViOme ORFeome comprises 253 constructs, together covering 88.8% of unique viral ORFs from nine viruses. The *supplementary table* provides information on all viral ORF constructs within the NeuroViOme ORFeome, including sequences, sequence configuration (open/closed) and vectors. The clones can be obtained from the authors. Clones for HSV-1 can additionally be obtained from the DNASU plasmid repository.

Optimization strategies included codon adaptation for gene synthesis for difficult or repetitive sequences. The ORF sequences of EBV_BWRF1.1, EBV_BVLF1, EBV_LF1, EBV_BALF3, HHV3_gp16 and the respective ORF 3B from the four enteroviruses were codon-optimized for *S. cerevisiae* to permit their synthesis. Additionally, the four ORF 3B sequences from the reference genomes were each placed in three tandem repeats separated by glycine linkers to obtain sequences permissible to synthesis. Importantly, these strategies faithfully retain the amino acid sequences of the encoded proteins and should therefore not impact the study of protein structure and cellular function, although potential unknown regulatory elements within the coding sequences may not be maintained. A modular cloning workflow compatible with Gateway recombination technology and a large collection of plasmids ensures that the NeuroViOme constructs can be readily deployed in a wide variety of downstream functional assays, including interaction screens, phenotypic assays and to subcellular localization studies to name just a few. The standardized construct design and use of identical vectors in these assays ensures that all results can be integrated in a meaningful way.

Discussion

The breadth of the NeuroViOme resource significantly extends beyond previous ORFeome projects that were limited to single viruses or narrow taxonomic groups(Calderwood et al. 2007; Rozenblatt-Rosen et al. 2012; Weller et al. 2023). By Integrating the coding repertoires of multiple neurotropic viruses into a single, standardized collection, in a flexible recombinational cloning system NeuroViOme enables cross-species and comparative virology approaches that were not previously feasible. For instance, it allows parallel interrogation of host–virus protein–protein interaction (PPI) networks to identify conserved and virus-specific strategies of host manipulation. These comparative studies can illuminate shared pathogenic mechanisms, such as the exploitation of RNA-binding proteins or stress granule components, as well as unique features that distinguish individual viral species.

Moreover, the comprehensive representation of viral coding sequences creates opportunities to explore synergistic or antagonistic effects of co-infection, which is particularly relevant in the context of neurodegeneration, where cumulative viral burden or sequential exposure to distinct pathogens has been proposed as a risk factor (Levine et al. 2023). The modular nature of the collection also facilitates multiplexed functional screens, enabling simultaneous interrogation of large viral protein sets in neuronal or glial models.

It must be noted that, although the NeuroViOme ORFeome provides broad coverage of viral coding sequences, certain aspects of viral gene expression remain outside the scope of this resource. The collection focuses on canonical protein-coding ORFs and therefore does not include alternative splice variants, non-coding regulatory elements, or accessory peptides that aregenerated through proteolytic processing during specific infection stages in addition to canonical cleavage products. In a few cases, synthesis of highly repetitive or GC-rich sequences required codon optimization, which preserves the encoded proteins but may differ from native transcriptional features within the coding sequence. These considerations reflect common constraints in large-scale ORFeome generation and do not diminish the utility of the resource.

Since the generation of this ORFeome was mainly motivated by our high throughput virus-host protein-protein interaction mapping effort (manuscript in preparation) the collection is also ideally suited for functional genomics and cell biology approaches. Beyond this, viral proteins can be expressed individually or in combinations to probe their combined effects on neuronal survival, protein aggregation, and innate immune signaling. In parallel, structural biology efforts can exploit the cloned ORFs for protein expression and structural analysis, accelerating the discovery of small-molecule inhibitors targeting key virus–host interfaces. The ORFeome further enables functional high-throughput screening (Pachano et al. 2025) and rapid hypothesis testing as well as comparative Perturb-seq style studies (Dixit et al. 2016). Naturally, ORF-level functional studies cannot replace studies with whole viruses but are a powerful and safe complement to interrogate the impact of individual or small groups of viral proteins. Collectively, these approaches will enable studies to elucidate how viruses influence neurodegenerative disease processes and support the development of novel antiviral or neuroprotective therapies.

Taken together we present NeuroViOme as a powerful resource for the standardized functional study of neurotrophic viruses. NeuroViOme captures the vast majority of full-length viral ORFs across nine neuro-associated viruses and provides one of the most comprehensive and experimentally ready viral ORFeome collections available to date and provides a powerful platform for understanding viral contribution to neurodegenerative diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13365-025-01303-5.

Acknowledgements This work was funded by The ALS Association, Prevention Program, Award ID 23-PP-669 and the Free State of Bavaria's AI for Therapy (AI4T) Initiative through the Institute of AI for Drug Discovery (AID).

Author contributions Project conception: PFB, CF, BW Experiments (ORF cloning etc.): BW, SR, A; MAC, Data analyses and evaluation: C-WL, BWFunding acquisition: PFB, CFManuscript writing: BW, PFB, CF.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information. ORFs will be distributed upon request to the corresponding authors.

Declarations

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

Altmann M, Altmann S, Falter C, Falter-Braun P (2018) High-quality yeast-2-hybrid interaction network mapping. Curr Protoc Plant Biol 3:e20067. https://doi.org/10.1002/cppb.20067

Altmann M, Altmann S, Rodriguez PA, Weller B, Elorduy Vergara L, Palme J, Marín-de la Rosa N, Sauer M, Wenig M, Villaécija-Aguilar JA, Sales J, Lin C-W, Pandiarajan R, Young V, Strobel A, Gross L, Carbonnel S, Kugler KG, Garcia-Molina A, Bassel GW, Falter C, Mayer KFX, Gutjahr C, Vlot AC, Grill E, Falter-Braun P (2020) Extensive signal integration by the phytohormone protein network. Nature 583:271–276. https://doi.org/10.1038/s41586-020-2460-0

Ames J, Yadavalli T, Suryawanshi R, Hopkins J, Agelidis A, Patil C, Fredericks B, Tseng H, Valyi-Nagy T, Shukla D (2021) OPTN is a host intrinsic restriction factor against neuroinvasive HSV-1 infection. Nat Commun 12:5401. https://doi.org/10.1038/s41467-021-25642-z

Basic M, Keubler LM, Buettner M, Achard M, Breves G, Schroder B, Smoczek A, Jorns A, Wedekind D, Zschemisch NH, Gunther C, Neumann D, Lienenklaus S, Weiss S, Hornef MW, Mahler M, Bleich A (2014) Norovirus triggered microbiota-driven mucosal inflammation in Interleukin 10-deficient mice. Inflamm Bowel Dis 20:431–443. https://doi.org/10.1097/01.MIB.0000441346.86827.ed

Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A (2022) Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 375:296–301. https://doi.org/10.1126/science.abj8222

Blandi L, Bertuccio P, Signorelli C, Brand H, Clemens T, Renzi C, Odone A (2025) Herpes zoster as risk factor for dementia: a matched cohort study over 20 years in a 10-million population in Italy. J Prev Alzheimers Dis 12:100167. https://doi.org/10.1016/j.tjpad.2025.100167

Braun P, Tasan M, Dreze M, Barrios-Rodiles M, Lemmens I, Yu H, Sahalie JM, Murray RR, Roncari L, de Smet A-S, Venkatesan K, Rual J-F, Vandenhaute J, Cusick ME, Pawson T, Hill DE, Tavernier J, Wrana JL, Roth FP, Vidal M (2009) An experimentally derived confidence score for binary protein-protein interactions. Nat Methods 6:91–97. https://doi.org/10.1038/nmeth.1281

Cadwell K, Patel KK, Maloney NS, Liu TC, Ng AC, Storer CE, Head RD, Xavier R, Stappenbeck TS, Virgin HW (2010) Virus-plus-susceptibility gene interaction determines crohn's disease gene Atg16L1 phenotypes in intestine. Cell 141:1135–1145. https://doi.org/10.1016/j.cell.2010.05.009

Cairns DM, Itzhaki RF, Kaplan DL (2022) Potential involvement of varicella Zoster virus in Alzheimer's disease via reactivation of

quiescent herpes simplex virus type 1. J Alzheimers Dis 88:1189–1200. https://doi.org/10.3233/JAD-220287

Calderwood MA, Venkatesan K, Xing L, Chase MR, Vazquez A, Holthaus AM, Ewence AE, Li N, Hirozane-Kishikawa T, Hill DE, Vidal M, Kieff E, Johannsen E (2007) Epstein-Barr virus and virus human protein interaction maps. Proc Natl Acad Sci USA 104:7606–7611. https://doi.org/10.1073/pnas.0702332104

Carfì A, Bernabei R, Landi F, Gemelli Against C-P-ACSG (2020) Persistent symptoms in patients after acute COVID-19. JAMA 324:603–605. https://doi.org/10.1001/jama.2020.12603

Celeste DB, Miller MS (2018) Reviewing the evidence for viruses as environmental risk factors for ALS: a new perspective. Cytokine 108:173–178. https://doi.org/10.1016/j.cyto.2018.04.010

Chooi WH, Winanto, Zeng Y, Lee CY, Lim ZQ, Gautam P, Chu JJH, Loh YH, Alonso S, Ng SY (2024) Enterovirus-A71 preferentially infects and replicates in human motor neurons, inducing neurodegeneration by ferroptosis. Emerg Microbes Infect 13:2382235. https://doi.org/10.1080/22221751.2024.2382235

Choutka J, Jansari V, Hornig M, Iwasaki A (2022) Unexplained post-acute infection syndromes. Nat Med 28:911–923. https://doi.org/10.1038/s41591-022-01810-6

de Chassey B, Navratil V, Tafforeau L, Hiet MS, Aublin-Gex A, Agaugue S, Meiffren G, Pradezynski F, Faria BF, Chantier T, Le Breton M, Pellet J, Davoust N, Mangeot PE, Chaboud A, Penin F, Jacob Y, Vidalain PO, Vidal M, Andre P, Rabourdin-Combe C, Lotteau V (2008) Hepatitis C virus infection protein network. Mol Syst Biol 4:230. https://doi.org/10.1038/msb.2008.66

De Chiara G, Marcocci ME, Civitelli L, Argnani R, Piacentini R, Ripoli C, Manservigi R, Grassi C, Garaci E, Palamara AT (2010) APP processing induced by herpes simplex virus type 1 (HSV-1) yields several APP fragments in human and rat neuronal cells. PLoS One 5:e13989. https://doi.org/10.1371/journal.pone.0013989

Dixit A, Parnas O, Li B, Chen J, Fulco CP, Jerby-Arnon L, Marjanovic ND, Dionne D, Burks T, Raychowdhury R, Adamson B, Norman TM, Lander ES, Weissman JS, Friedman N, Regev A (2016) Perturb-Seq: dissecting molecular circuits with scalable single-cell RNA profiling of pooled genetic screens. Cell 167:1853-1866.e17. https://doi.org/10.1016/j.cell.2016.11.038

Eyting M, Xie M, Michalik F, Hess S, Chung S, Geldsetzer P (2025) A natural experiment on the effect of herpes zoster vaccination on dementia. Nature 641:438–446. https://doi.org/10.1038/s41586-025-08800-x

Garcia-Montojo M, Fathi S, Rastegar C, Simula ER, Doucet-O'Hare T, Cheng YHH, Abrams RPM, Pasternack N, Malik N, Bachani M, Disanza B, Maric D, Lee MH, Wang H, Santamaria U, Li W, Sampson K, Lorenzo JR, Sanchez IE, Mezghrani A, Li Y, Sechi LA, Pineda S, Heiman M, Kellis M, Steiner J, Nath A (2024) TDP-43 proteinopathy in ALS is triggered by loss of ASRGL1 and associated with HML-2 expression. Nat Commun 15:4163. https://doi.org/10.1038/s41467-024-48488-7

Greenhalgh T, Sivan M, Perlowski A, Nikolich JZ (2024) Long COVID: a clinical update. Lancet 404:707–724. https://doi.org/10.1016/S0140-6736(24)01136-X

Gulbahce N, Yan H, Dricot A, Padi M, Byrdsong D, Franchi R, Lee DS, Rozenblatt-Rosen O, Mar JC, Calderwood MA, Baldwin A, Zhao B, Santhanam B, Braun P, Simonis N, Huh KW, Hellner K, Grace M, Chen A, Rubio R, Marto JA, Christakis NA, Kieff E, Roth FP, Roecklein-Canfield J, DeCaprio JA, Cusick ME, Quackenbush J, Hill DE, Munger K, Vidal M, Barabasi AL (2012) Viral perturbations of host networks reflect disease etiology. PLoS Comput Biol 8:e1002531. https://doi.org/10.1371/journal.pcbi.1002531

Honkimaa A, Laine P, Suppula J, Tynninen O, Saarela M, Laakso SM, Hetemaki I, Liimatainen H, Auvinen P, Auvinen E (2024) Exploring JC polyomavirus sequences and human gene expression in brain tissue of patients with progressive multifocal leukoencephalopathy. J Infect Dis 230:e732–e736. https://doi.org/10.1093/infdis/jiae066

Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA (1997) Herpes simplex virus type 1 in brain and risk of alzheimer's disease. Lancet 349:241–244. https://doi.org/10.1016/S0140-6736(96)10149-5

Kim DK, Weller B, Lin CW, Sheykhkarimli D, Knapp JJ, Dugied G, Zanzoni A, Pons C, Tofaute MJ, Maseko SB, Spirohn K, Laval F, Lambourne L, Kishore N, Rayhan A, Sauer M, Young V, Halder H, la Rosa NM, Pogoutse O, Strobel A, Schwehn P, Li R, Rothballer ST, Altmann M, Cassonnet P, Cote AG, Vergara LE, Hazelwood I, Liu BB, Nguyen M, Pandiarajan R, Dohai B, Coloma PAR, Poirson J, Giuliana P, Willems L, Taipale M, Jacob Y, Hao T, Hill DE, Brun C, Twizere JC, Krappmann D, Heinig M, Falter C, Aloy P, Demeret C, Vidal M, Calderwood MA, Roth FP, Falter-Braun P (2022) A proteome-scale map of the SARS-CoV-2-human contactome. Nat Biotechnol. https://doi.org/10.1038/s41587-022-01475-z

Leblanc P, Vorberg IM (2022) Viruses in neurodegenerative diseases: more than just suspects in crimes. PLoS Pathog 18:e1010670. https://doi.org/10.1371/journal.ppat.1010670

Levine KS, Leonard HL, Blauwendraat C, Iwaki H, Johnson N, Bandres-Ciga S, Ferrucci L, Faghri F, Singleton AB, Nalls MA (2023) Virus exposure and neurodegenerative disease risk across national biobanks. Neuron 111:1086-1093 e2. https://doi.org/10.1016/j.neuron.2022.12.029

Li J, Zhang G, Sun Q, Zhang K, Lu H, Xiao J, Han Z, Zhao H, Xu W, Zhang Y, Liu Z (2022) Pathological characteristics of echovirus 30 infection in a mouse model. J Virol 96:e0012922. https://doi.org/10.1128/jvi.00129-22

Luck K, Kim D-K, Lambourne L, Spirohn K, Begg BE, Bian W, Brignall R, Cafarelli T, Campos-Laborie FJ, Charloteaux B, Choi D, Coté AG, Daley M, Deimling S, Desbuleux A, Dricot A, Gebbia M, Hardy MF, Kishore N, Knapp JJ, Kovács IA, Lemmens I, Mee MW, Mellor JC, Pollis C, Pons C, Richardson AD, Schlabach S, Teeking B, Yadav A, Babor M, Balcha D, Basha O, Bowman-Colin C, Chin S-F, Choi SG, Colabella C, Coppin G, D'Amata C, De Ridder D, De Rouck S, Duran-Frigola M, Ennajdaoui H, Goebels F, Goehring L, Gopal A, Haddad G, Hatchi E, Helmy M, Jacob Y, Kassa Y, Landini S, Li R, van Lieshout N, MacWilliams A, Markey D, Paulson JN, Rangarajan S, Rasla J, Rayhan A, Rolland T, San-Miguel A, Shen Y, Sheykhkarimli D, Sheynkman GM, Simonovsky E, Taşan M, Tejeda A, Tropepe V, Twizere J-C, Wang Y, Weatheritt RJ, Weile J, Xia Y, Yang X, Yeger-Lotem E, Zhong Q, Aloy P, Bader GD, De Las Rivas J, Gaudet S, Hao T, Rak J, Tavernier J, Hill DE, Vidal M, Roth FP, Calderwood MA (2020) A reference map of the human binary protein interactome. Nature 580:402–408. https://doi.org/10.1038/s41586-020-2188-x

Luo Z, Su R, Wang W, Liang Y, Zeng X, Shereen MA, Bashir N, Zhang Q, Zhao L, Wu K, Liu Y, Wu J (2019) EV71 infection induces neurodegeneration via activating TLR7 signaling and IL-6 production. PLoS Pathog 15:e1008142. https://doi.org/10.1371/journal.ppat.1008142

Mukhtar MS, Carvunis AR, Dreze M, Epple P, Steinbrenner J, Moore J, Tasan M, Galli M, Hao T, Nishimura MT, Pevzner SJ, Donovan SE, Ghamsari L, Santhanam B, Romero V, Poulin MM, Gebreab F, Gutierrez BJ, Tam S, Monachello D, Boxem M, Harbort CJ, McDonald N, Gai L, Chen H, He Y, Effectoromics EU, Vandenhaute C, Roth J, Hill FP, Ecker DE, Vidal JR, Beynon M, Braun J, Dangl P JL (2011) Independently evolved virulence effectors converge onto hubs in a plant immune system network. Science 333:596–601. https://doi.org/10.1126/science.1203659

Osborne R, Rehneke L, Lehmann S, Roberts J, Altmann M, Altmann S, Zhang Y, Kopff E, Dominguez-Ferreras A, Okechukwu E, Sergaki C, Rich-Griffin C, Ntoukakis V, Eichmann R, Shan W, Falter-Braun P, Schafer P (2023) Symbiont-host interactome mapping

reveals effector-targeted modulation of hormone networks and activation of growth promotion. Nat Commun 14:4065. https://doi.org/10.1038/s41467-023-39885-5

Pachano T, Leng H, Dugied G, Tribble T, Loubiere V, Rauh F, Lee Y, Schleiffer A, Young V, Weller B, Lyons EA, Hass MR, Kottayan LC, Weirauch MT, Fuxman Bass JI, Newton HJ, Ensminger AW, Falter-Braun P, Schramek D, Stark A, Taipale M (2025) Systematic discovery of pathogen effector functions across human pathogens and pathways. bioRxiv. https://doi.org/10.1101/2025.11.17.687821

Park SJ, Jin U, Park SM (2021) Interaction between coxsackievirus B3 infection and alpha-synuclein in models of Parkinson's disease. PLoS Pathog 17:e1010018. https://doi.org/10.1371/journal.ppat.1010018

Patrick KL, Bell SL, Weindel CG, Watson RO (2019) Exploring the "Multiple-Hit Hypothesis" of neurodegenerative disease: bacterial infection comes up to bat. Front Cell Infect Microbiol 9:138. https://doi.org/10.3389/fcimb.2019.00138

Pellet J, Tafforeau L, Lucas-Hourani M, Navratil V, Meyniel L, Achaz G, Guironnet-Paquet A, Aublin-Gex A, Caignard G, Cassonnet P, Chaboud A, Chantier T, Deloire A, Demeret C, Le Breton M, Neveu G, Jacotot L, Vaglio P, Delmotte S, Gautier C, Combet C, Deleage G, Favre M, Tangy F, Jacob Y, Andre P, Lotteau V, Rabourdin-Combe C, Vidalain PO (2010) Viralorfeome: an integrated database to generate a versatile collection of viral ORFs. Nucleic Acids Res 38:D371–D378. https://doi.org/10.1093/nar/gkp1000

Rolfs A, Montor WR, Yoon SS, Hu Y, Bhullar B, Kelley F, McCarron S, Jepson DA, Shen B, Taycher E, Mohr SE, Zuo D, Williamson J, Mekalanos J, Labaer J (2008) Production and sequence validation of a complete full length ORF collection for the pathogenic bacterium *vibrio cholerae*. Proc Natl Acad Sci U S A 105:4364–4369. https://doi.org/10.1073/pnas.0712049105

Rozenblatt-Rosen O, Deo RC, Padi M, Adelmant G, Calderwood MA, Rolland T, Grace M, Dricot A, Askenazi M, Tavares M, Pevzner SJ, Abderazzaq F, Byrdsong D, Carvunis AR, Chen AA, Cheng J, Correll M, Duarte M, Fan C, Feltkamp MC, Ficarro SB, Franchi R, Garg BK, Gulbahce N, Hao T, Holthaus AM, James R, Korkhin A, Litovchick L, Mar JC, Pak TR, Rabello S, Rubio R, Shen Y, Singh S, Spangle JM, Tasan M, Wanamaker S, Webber JT, Roecklein-Canfield J, Johannsen E, Barabasi AL, Beroukhim R, Kieff E, Cusick ME, Hill DE, Munger K, Marto JA, Quackenbush J, Roth FP, DeCaprio JA, Vidal M (2012) Interpreting cancer genomes using systematic host network perturbations by tumour virus proteins. Nature 487:491–5. https://doi.org/10.1038/nature11288

Salazar-Grueso EF, Roos RP (1995) Amyotrophic lateral sclerosis and viruses. Clin Neurosci 3:360–367

Seiler CY, Park JG, Sharma A, Hunter P, Surapaneni P, Sedillo C, Field J, Algar R, Price A, Steel J, Throop A, Fiacco M, LaBaer J (2014) DNASU plasmid and PSI:biology-materials repositories: resources to accelerate biological research. Nucleic Acids Res 42:D1253–D1260. https://doi.org/10.1093/nar/gkt1060

Steiner JP, Bachani M, Malik N, DeMarino C, Li W, Sampson K, Lee MH, Kowalak J, Bhaskar M, Doucet-O'Hare T, Garcia-Montojo M, Cowen M, Smith B, Reoma LB, Medina J, Brunel J, Pierquin J, Charvet B, Perron H, Nath A (2022) Human endogenous retrovirus K envelope in spinal fluid of amyotrophic lateral sclerosis is toxic. Ann Neurol 92:545–561. https://doi.org/10.1002/ana.26452

Tiwari D, Mittal N, Jha HC (2022) Unraveling the links between neurodegeneration and Epstein-Barr virus-mediated cell cycle dysregulation. Curr Res Neurobiol 3:100046. https://doi.org/10.1016/j.crneur.2022.100046

Varjosalo M, Sacco R, Stukalov A, van Drogen A, Planyavsky M, Hauri S, Aebersold R, Bennett KL, Colinge J, Gstaiger M, Superti-Furga G (2013) Interlaboratory reproducibility of large-scale human protein-complex analysis by standardized AP-MS. Nat Methods 10:307–14. https://doi.org/10.1038/nmeth.2400

Vogt MR, Wright PF, Hickey WF, De Buysscher T, Boyd KL, Crowe JE Jr. (2022) Enterovirus D68 in the anterior horn cells of a child with acute flaccid myelitis. N Engl J Med 386:2059–2060. https://doi.org/10.1056/NEJMc2118155

Walhout AJ, Temple GF, Brasch MA, Hartley JL, Lorson MA, van den Heuvel S, Vidal M (2000) GATEWAY recombinational cloning: application to the cloning of large numbers of open reading frames or ORFeomes. Methods Enzymol 328:575–92

Wan Q, Song D, Li H, He ML (2020) Stress proteins: the biological functions in virus infection, present and challenges for target-based antiviral drug development. Signal Transduct Target Ther 5:125. https://doi.org/10.1038/s41392-020-00233-4

Weller B, Lin CW, Pogoutse O, Sauer M, de la Marin- Rosa N, Strobel A, Young V, Knapp JJ, Rayhan A, Falter C, Kim DK, Roth FP, Falter-Braun P (2023) A resource of human coronavirus protein-coding sequences in a flexible, multipurpose Gateway Entry clone collection. G3 Genes Genomes Genet. https://doi.org/10.1093/g3journal/jkad105

Wessling R, Epple P, Altmann S, He Y, Yang L, Henz SR, McDonald N, Wiley K, Bader KC, Glasser C, Mukhtar MS, Haigis S, Ghamsari L, Stephens AE, Ecker JR, Vidal M, Jones JD, Mayer KF, Ver Loren van Themaat E, Weigel D, Schulze-Lefert P, Dangl JL, Panstruga R, Braun P (2014) Convergent targeting of a common host protein-network by pathogen effectors from three kingdoms of life. Cell Host Microbe 16:364–75. https://doi.org/10.1016/j.chom.2014.08.004

Wo X, Yuan Y, Xu Y, Chen Y, Wang Y, Zhao S, Lin L, Zhong X, Wang Y, Zhong Z, Zhao W (2021) TAR DNA-binding protein 43 is cleaved by the protease 3 C of enterovirus A71. Virol Sin 36:95–103. https://doi.org/10.1007/s12250-020-00262-x

Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 429:95–100. https://doi.org/10.1016/j.neulet.2007.09.077

Xue YC, Liu H, Mohamud Y, Bahreyni A, Zhang J, Cashman NR, Luo H (2022) Sublethal enteroviral infection exacerbates disease progression in an ALS mouse model. J Neuroinflammation 19:16. https://doi.org/10.1186/s12974-022-02380-7

Yu X, Bian X, Throop A, Song L, Moral LD, Park J, Seiler C, Fiacco M, Steel J, Hunter P, Saul J, Wang J, Qiu J, Pipas JM, LaBaer J (2014) Exploration of panviral proteome: high-throughput cloning and functional implications in virus-host interactions. Theranostics 4:808–822. https://doi.org/10.7150/thno.8255

Zhou Y, Liu Y, Gupta S, Paramo MI, Hou Y, Mao C, Luo Y, Judd J, Wierbowski S, Bertolotti M, Nerkar M, Jehi L, Drayman N, Nicolaescu V, Gula H, Tay S, Randall G, Lis JT, Feschotte C, Erzurum SC, Cheng F, Yu H (2022) A comprehensive SARS-CoV-2-human protein-protein interactome network identifies pathobiology and host-targeting therapies for COVID-19. Res Sq. https://doi.org/10.21203/rs.3.rs-1354127/v2

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.