



18th International Symposium on NeuroVirology

**Human Endogenous retroviruses (HERVs) express neuropathogenic proteins, which can be activated by environmental pathogens:
a post-infectious HERV-driven disease concept**

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Declared conflict of interest: Hervé Perron is presently CSO of Geneuro.

Human Endogenous Retroviruses

Friend

or

Foe ?



IMMUNOGENOMICS

Regulatory evolution of innate immunity through co-option of endogenous retroviruses

Edward B. Chuong, Nels C. Elde,*† Cédric Feschotte*†

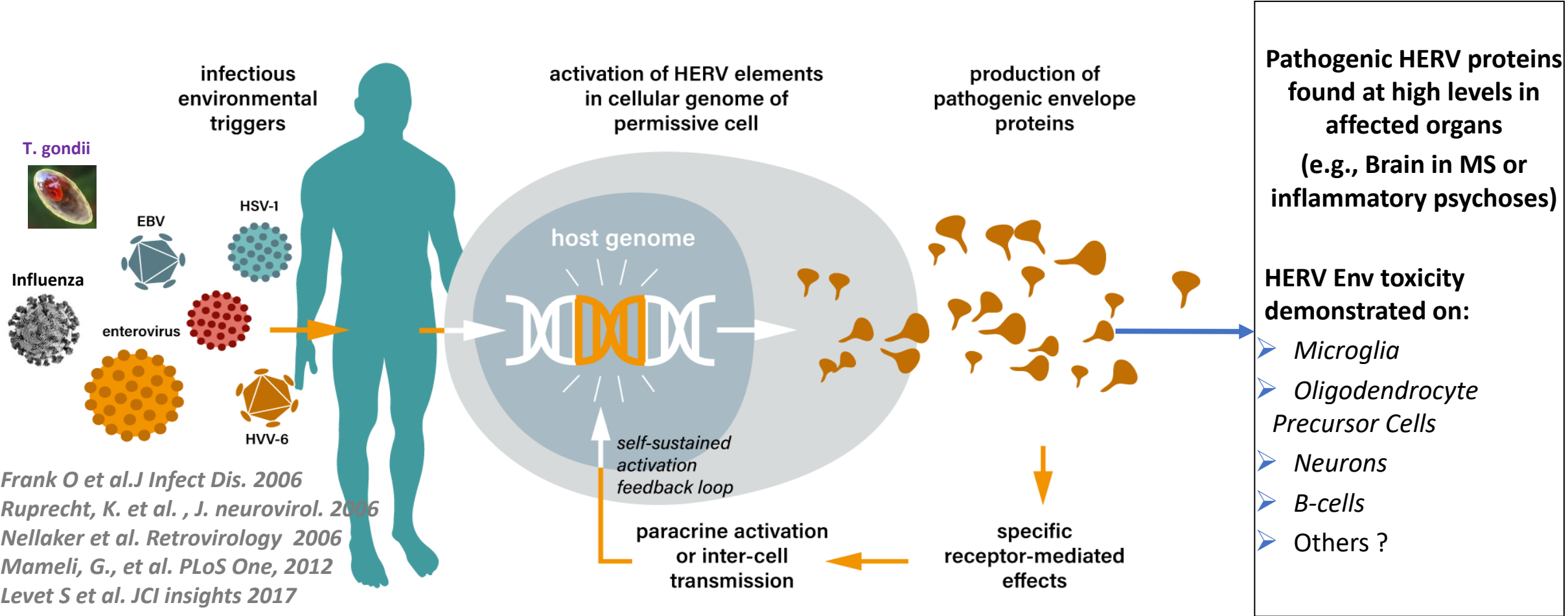


The enemy within: dormant retroviruses awaken

Michael E Engel & Scott W Hiebert
Nature Medicine 16, 517–518 (2010)

Environmental infectious factors can activate HERV elements

HERVs may be a key missing link between viral infections and poorly understood autoimmune / neurodegenerative diseases



Frank O et al. *J Infect Dis.* 2006
 Ruprecht, K. et al. , *J. neurovirol.* 2006
 Nellaker et al. *Retrovirology* 2006
 Marnett, G., et al. *PLoS One*, 2012
 Levet S et al. *JCI insights* 2017
 Charvet et al. *Frontiers Immunol*, 2018

Rolland et al. *J. immunol.* 2006; Kremer et al. *Ann. Neurol.* 2013; Levet et al. *JCI Insights* 2016
 Kremer et al. *PNAS* 2019 ; Johansson et al. *Sci. Adv.* 2020

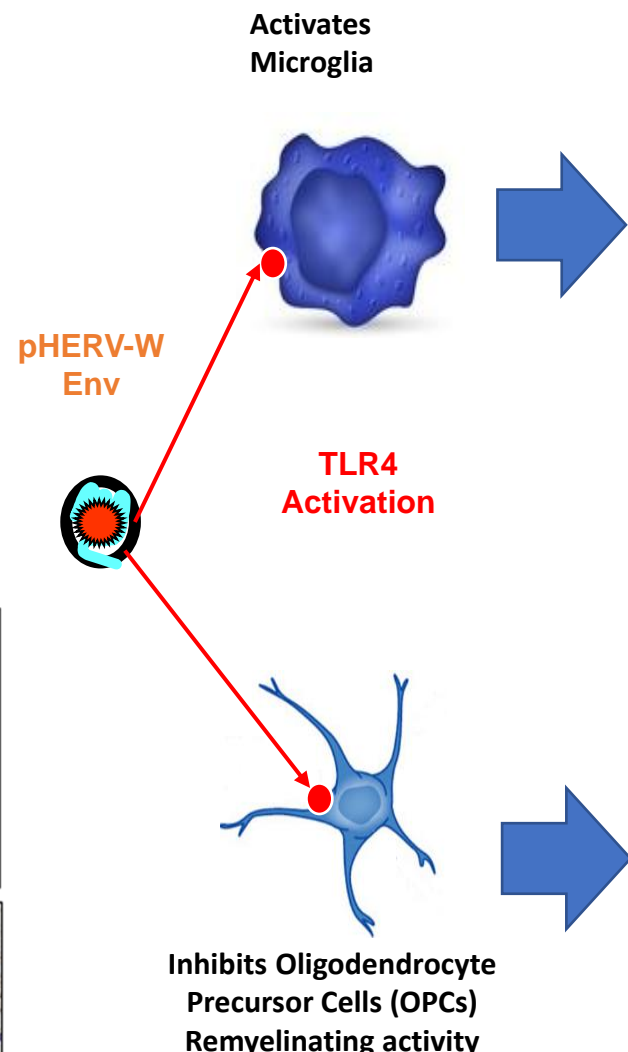
Environmental viruses in MS epidemiology

- Kaiser J (2022) Study of soldiers implicates **common virus as MS trigger**. Science 375:133. doi: 10.1126/science.ada0059
 - *“it’s still an association,” “and the study doesn’t explain why most people who get EBV don’t develop MS”* (<https://www.science.org/content/article/two-decades-soldiers-medical-records-implicate-common-virus-multiple-sclerosis>)
- Hrastelj J et al. (2022) A role for the **Epstein-Barr virus in multiple sclerosis aetiology?** J Neurol 269:3962-3963. doi: 10.1007/s00415-022-11177-w
- Voumvourakis KI et al. (2022) **Human herpesvirus 6 infection** as a trigger of multiple sclerosis: an update of recent literature. BMC Neurol 22:57. doi: 10.1186/s12883-022-02568-7
 - **Activating HERVs:**
- Latifi T et al. (2022) The role of human endogenous retroviruses (HERVs) in Multiple Sclerosis and the plausible **interplay between HERVs, Epstein-Barr virus infection, and vitamin D**. Mult Scler Relat Disord 57:103318. doi: 10.1016/j.msard.2021.103318
- Charvet B et al. (2018) **Induction of Proinflammatory Multiple Sclerosis-Associated Retrovirus (HERV-W) Envelope Protein by Human Herpesvirus-6A and CD46 Receptor Engagement**. Front Immunol 9:2803. doi: 10.3389/fimmu.2018.02803
- Mameli G et al. (2012) Expression and **activation by Epstein Barr virus of human endogenous retroviruses-W** in blood cells and astrocytes: inference for multiple sclerosis. PLoS One 7:e44991. doi: 10.1371/journal.pone.0044991

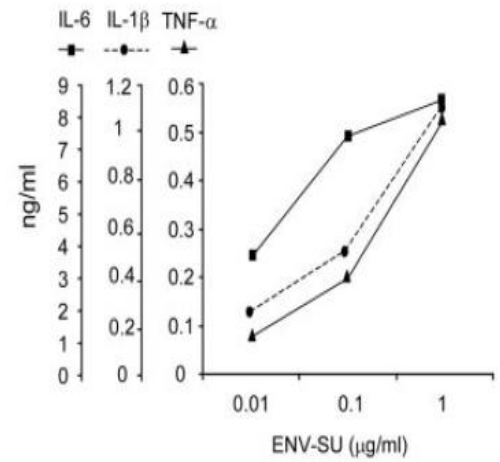
HERV-W Env activates microglia and inhibits differentiation of oligodendrocyte precursor cells

pHERV-W ENV reproduces pathogenic hallmarks of Multiple Sclerosis

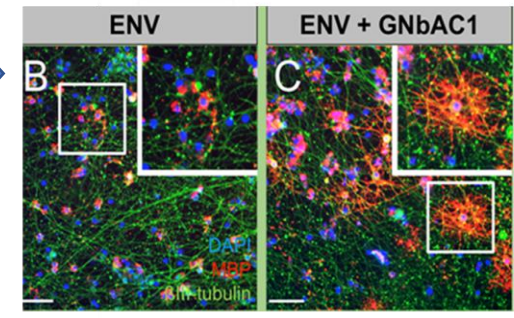
Kremer et al., Ann. Neurol, 2013;
Göttle et al. Glia 2019;
Kremer et al. PNAS 2019
VanHorsssen et al. MSARD 2016



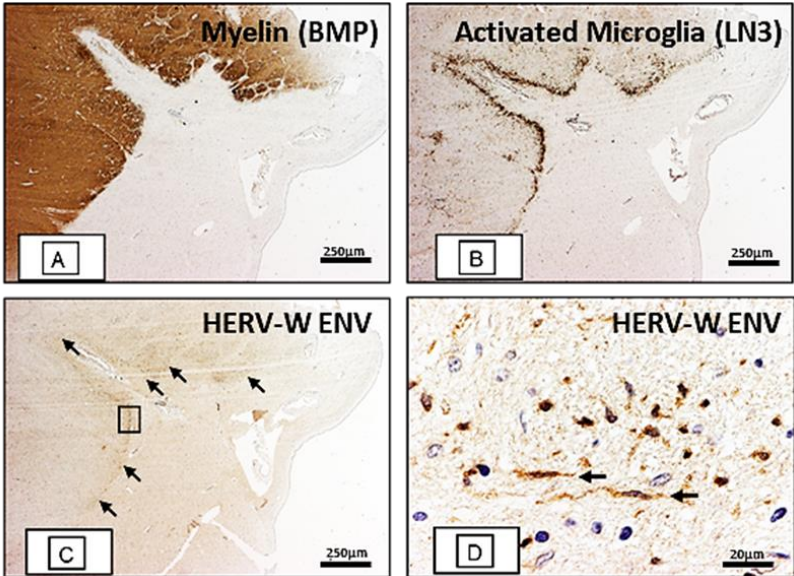
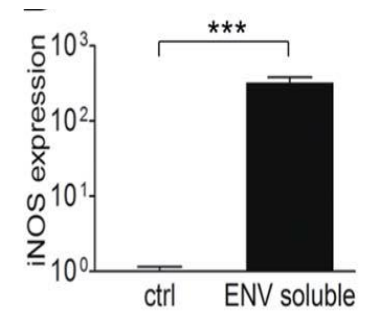
Release of pro-inflammatory cytokines



Inhibits Myelin Basic Protein (MBP)



Induces Oxidative stress



Environmental viruses in Schizophrenia

- Moreno JL et al. (2011) **Maternal influenza** viral infection causes schizophrenia-like alterations of 5-HT(2)A and mGlu(2) receptors **in the adult offspring**. J Neurosci 31:1863-1872. doi: 10.1523/JNEUROSCI.4230-10.2011
- Andreou D et al. (2021) **Cytomegalovirus infection** associated with smaller dentate gyrus in men with severe mental illness. Brain Behav Immun 96:54-62. doi: 10.1016/j.bbi.2021.05.009
- Burkhardt E et al. (2021) **Toxoplasma gondii, Herpesviridae and long-term risk** of transition to first-episode psychosis in an ultra high-risk sample. Schizophr Res 233:24-30. doi: 10.1016/j.schres.2021.06.012
- Cheng JS et al. (2021) **Hepatitis C-associated late-onset schizophrenia**: a nationwide, population-based cohort study. J Psychiatry Neurosci 46:E583-E591. doi: 10.1503/jpn.200154
- **Activating HERVs:**
 - Karlsson H et al. (2001) **Retroviral RNA identified in the cerebrospinal fluids** and brains of individuals with schizophrenia. Proc Natl Acad Sci U S A 98:4634-4639. doi: 10.1073/pnas.061021998
 - Nellaker C et al. (2006) **Transactivation of elements in the human endogenous retrovirus W family by viral infection**. Retrovirology 3:44. doi: 10.1186/1742-4690-3-44
 - Leboyer M et al. (2013) **Human endogenous retrovirus type W (HERV-W) in schizophrenia**: a new avenue of research at the gene-environment interface. World J Biol Psychiatry 14:80-90. doi: 10.3109/15622975.2010.601760

HERV-W ENV modulates the central role of microglia in psychotic disease associated with inflammation

Certain infectious agents acting during different periods of life transactivate HERV-W, thereby inducing chronic inflammation and synaptic displacement of GluN2b receptors

Environment

Exposition to infectious agents, stress and toxins

Infections

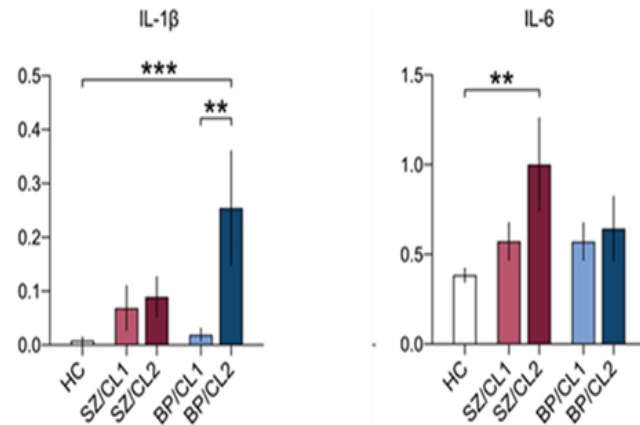
CMV
HSV-1
T. gondii
...

Activation of
HERV-W

HERV Genetics

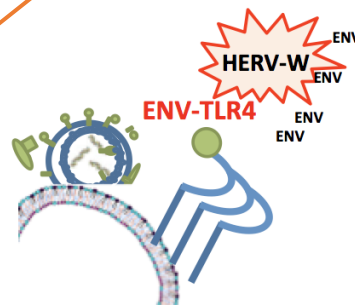
Non-ubiquitous/unfixed HERV copies
Epigenetic control
Interferon pathways response
Immuno-genetics
HLA, TLRs...

Human Endogenous retrovirus (HERV-W)



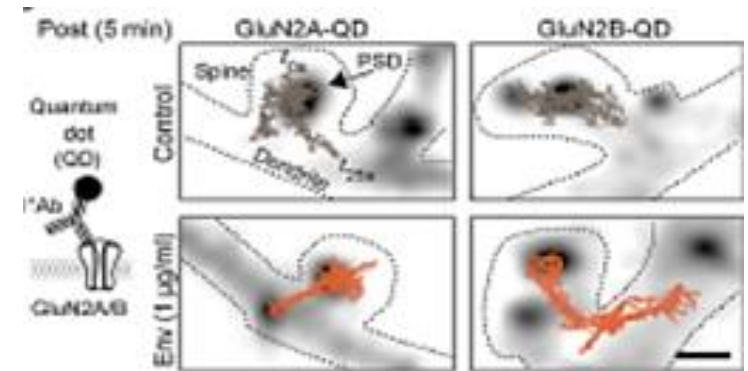
Low-grade Inflammation
IL1-Beta, IL-6, TNF-α CRP

Tamouza et al. *Transl. Psychiatry*, 2021



Microglia

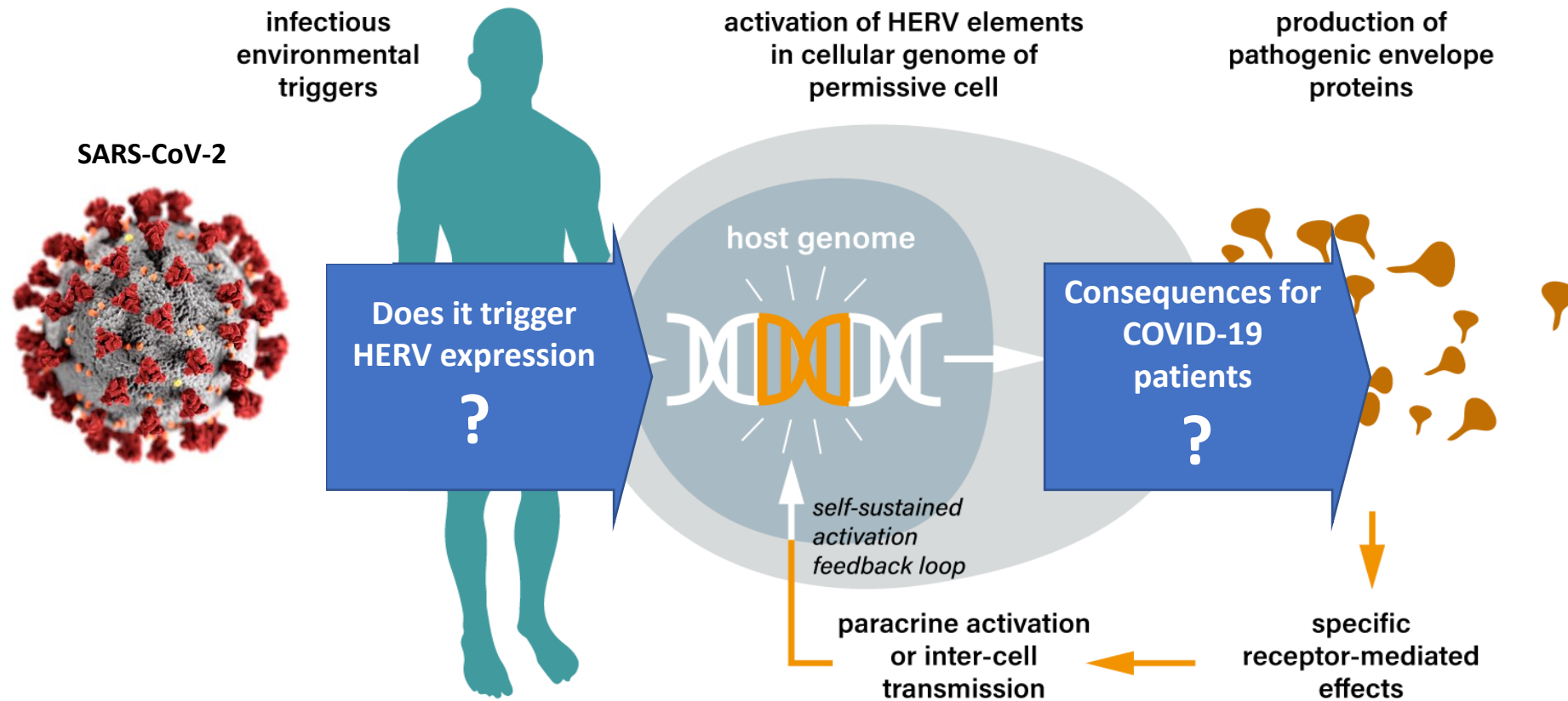
Perron et al, *Biol. Psychiatry* 2008 & *Transl. Psychiatry*, 2012



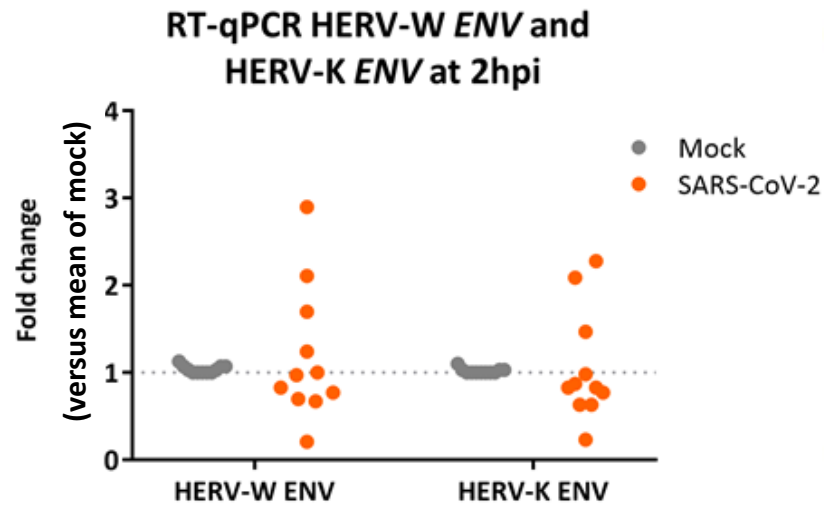
Functional loss of GluN2B receptors
via dispersal from synapses

Johansson et al. *Science advances* 2020

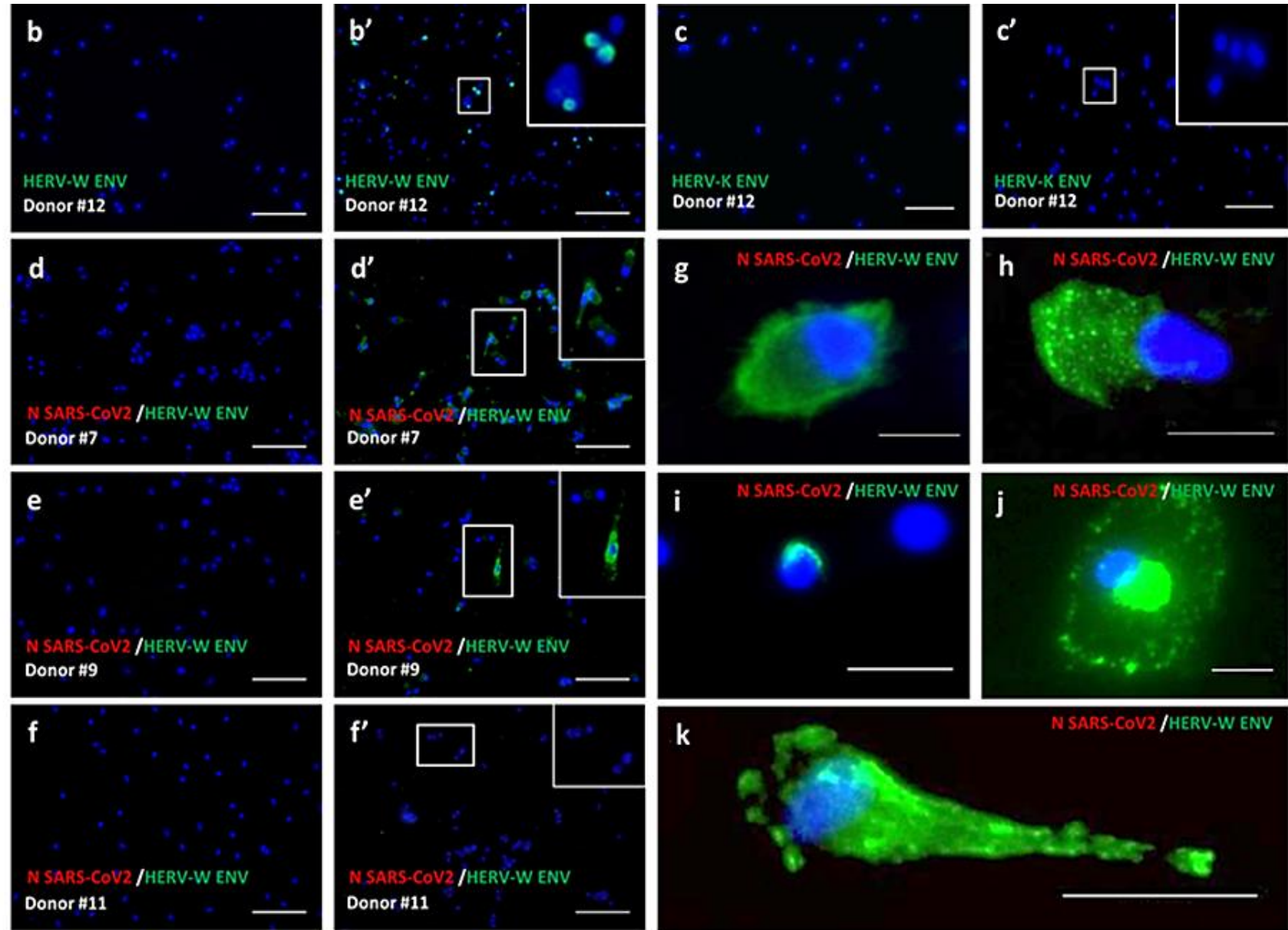
Environmental infectious factors can activate HERV elements playing a critical role at the Gene/environment interface



SARS-CoV2 is a potent activator of some HERV elements



Charvet et al, 2022 Submitted

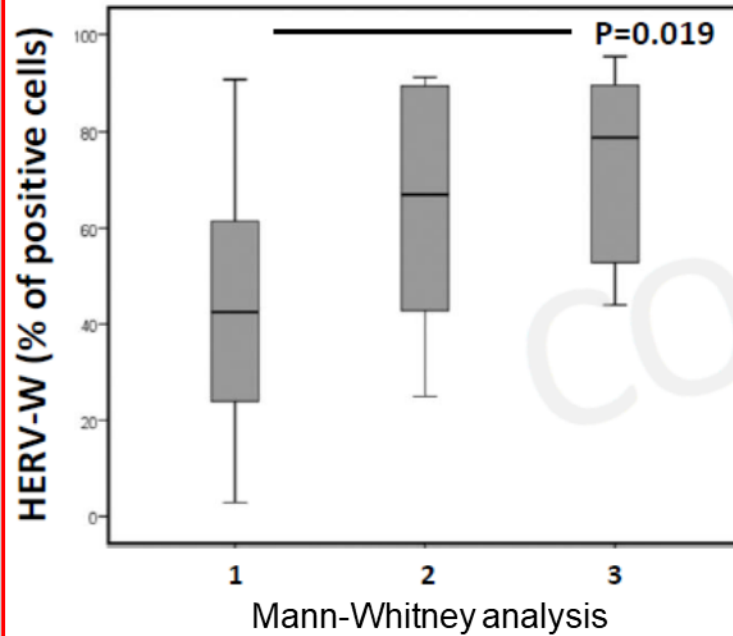


HERV-W Env in COVID-19 patients

Detection of ENV surface antigen on lymphocytes and of soluble antigen in plasma

HERV W protein (Lymphocytes)

Cytofluorometry

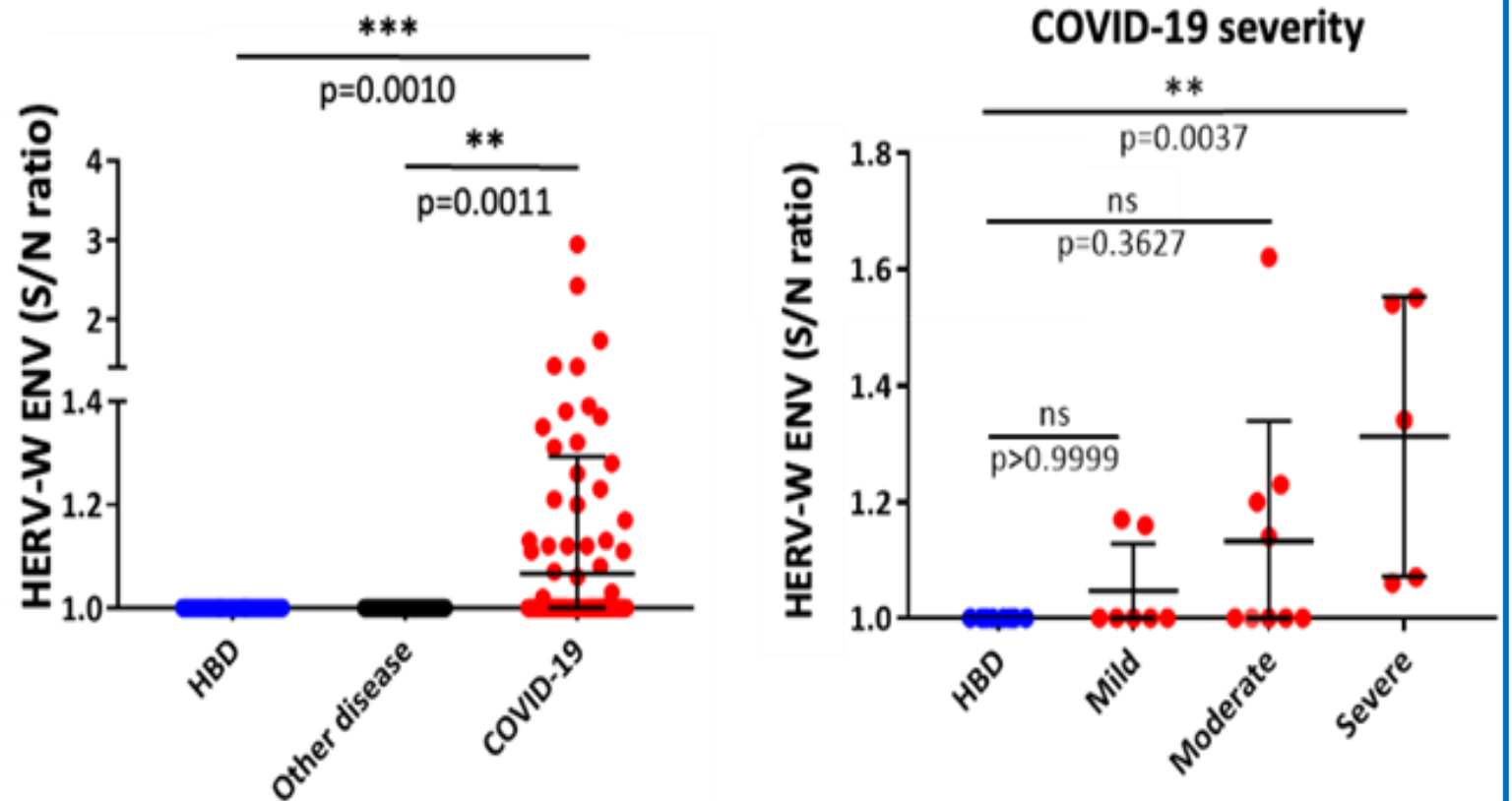


Evolution over time

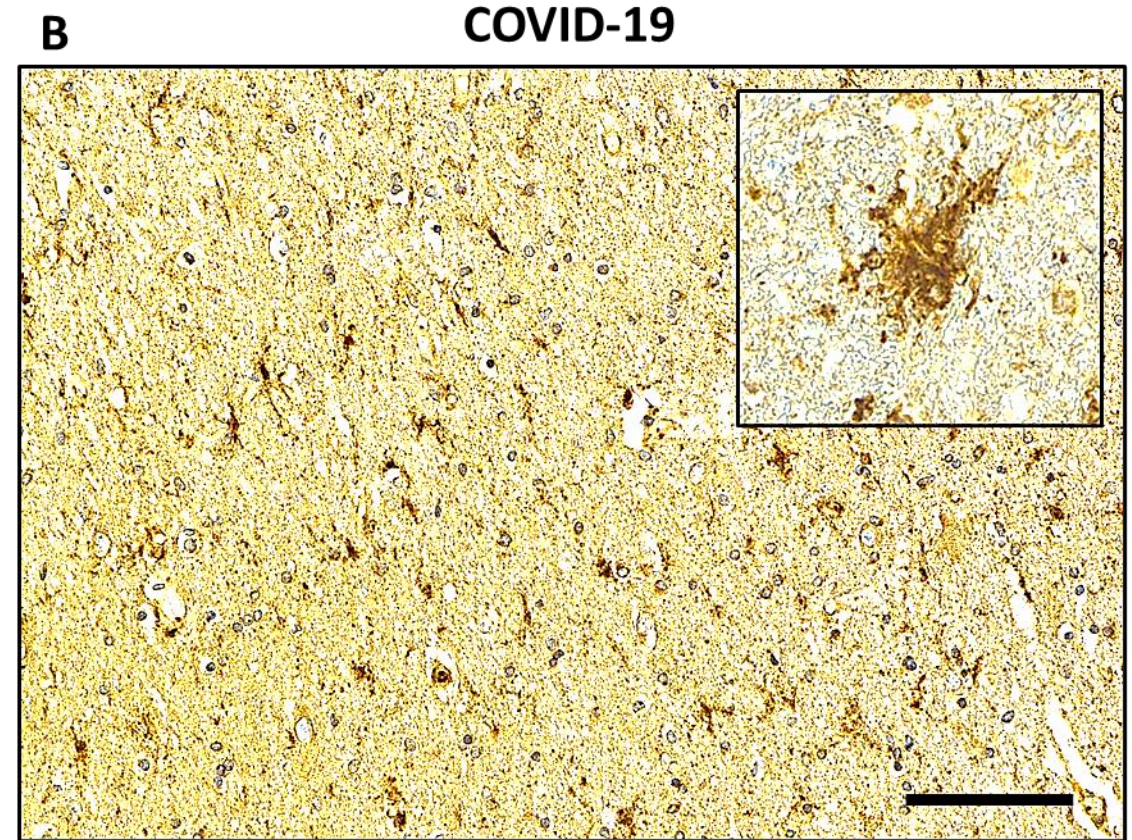
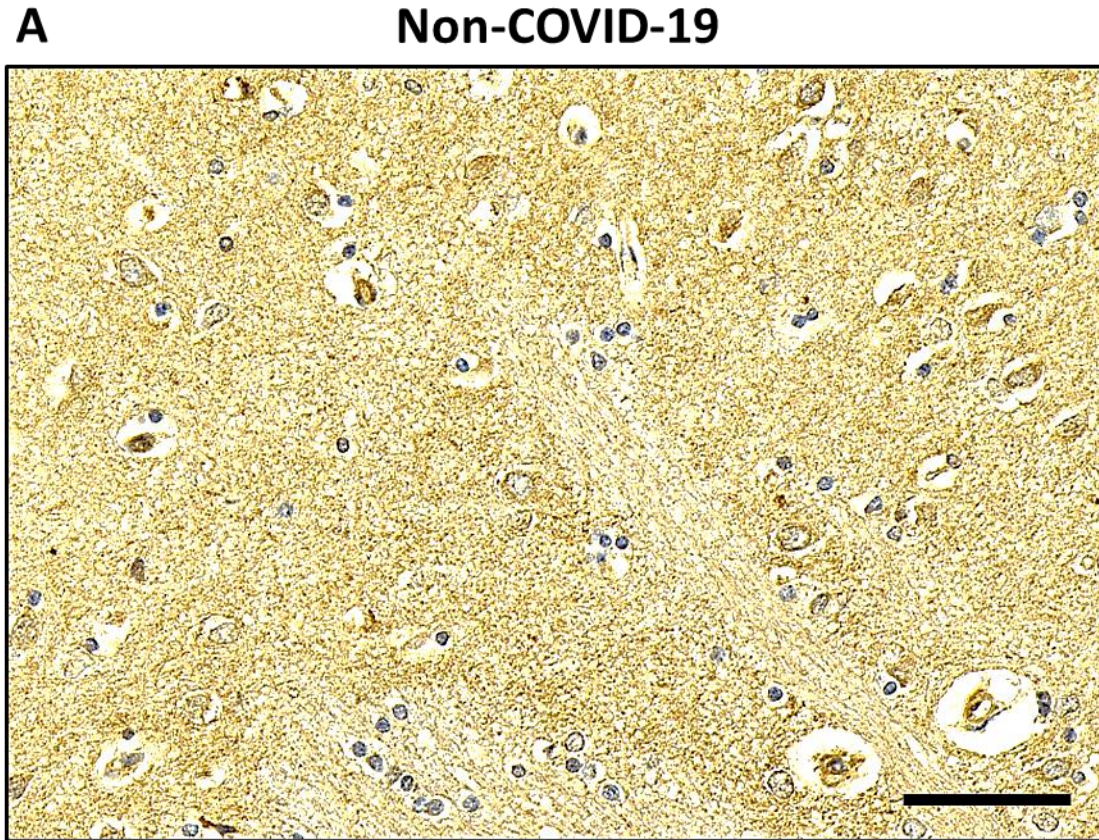
1. No air support
2. VMK / nasal cannula
3. Non-invasive ventilation / C-PAP

HERV-W ENV soluble antigen (Plasma)

Immunocapillary WB (Wes)



Activated HERV-W in the brain of patients with COVID-19

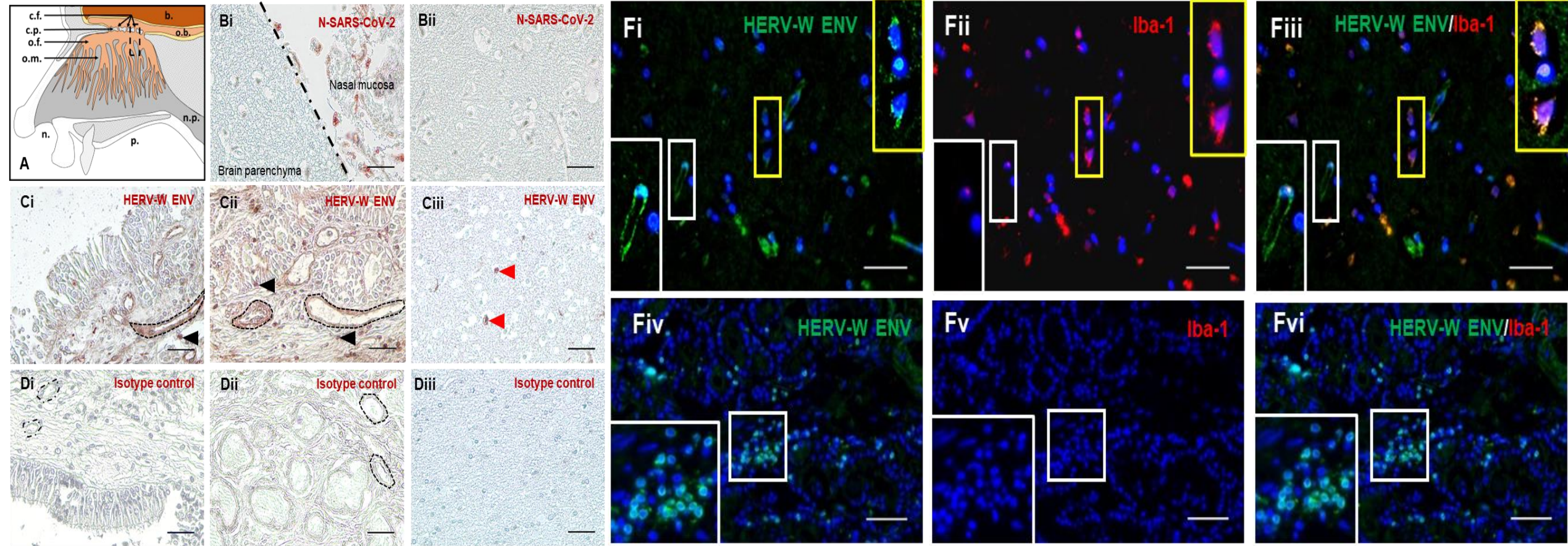


# Case	Age/Sex	PMI (hrs)	
Control 6	54/M	15	HTN, CAD with prior MI and coronary stent placement, smoking (1ppd for ~30 yrs, quit 5 years prior to death), colorectal tumor resection (benign)

# Case	Age/Sex	PMI (hrs)	Past Medical Hx	Recent Hx	Days from symptom onset to death
Case 1	73/M	38	HTN, obesity	Pneumonia, renal failure, pericardial effusion, arrhythmia, hospitalized for 8 days intubated for 3 days	16 days

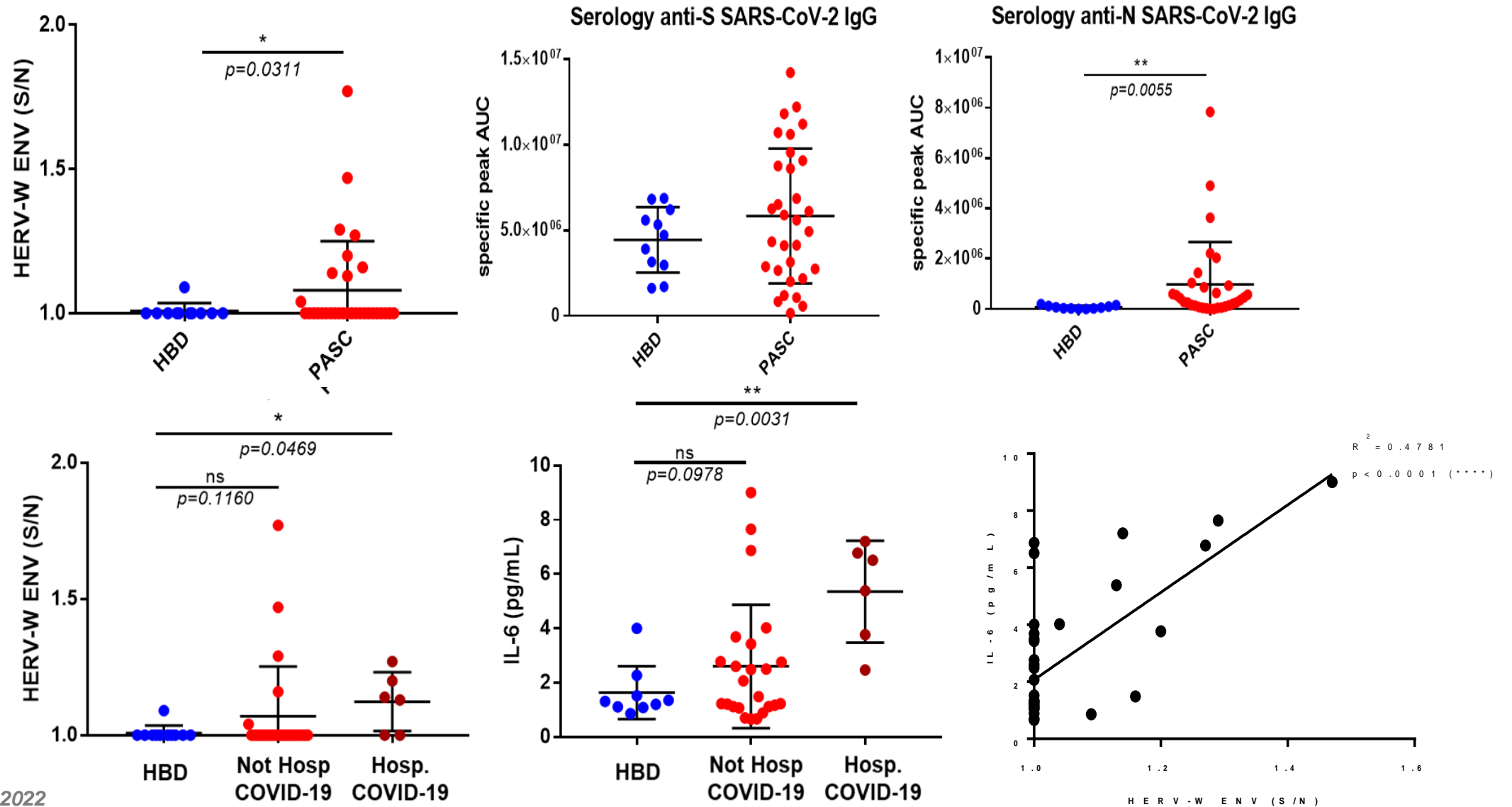
HERV-W Env in COVID-19 patients

Detection in brain microglia in the absence of SARS-CoV-2 detection



HERV-W Env in Post-COVID patients: Pilot series from Chicago, USA

Detection of ENV soluble antigen in serum versus IL-6 and SARS-CoV-2 serology



HERV-W Env is present in a sub-group of patients with Post-COVID

Post/Long COVID patients represent a heterogeneous nosological entity that can be stratified by biomarkers:

Different pathogenic drivers and subtypes of Post-COVID syndrome ?

Main groups defined by biomarkers:

A. Ig anti-SARS-CoV-2 N+

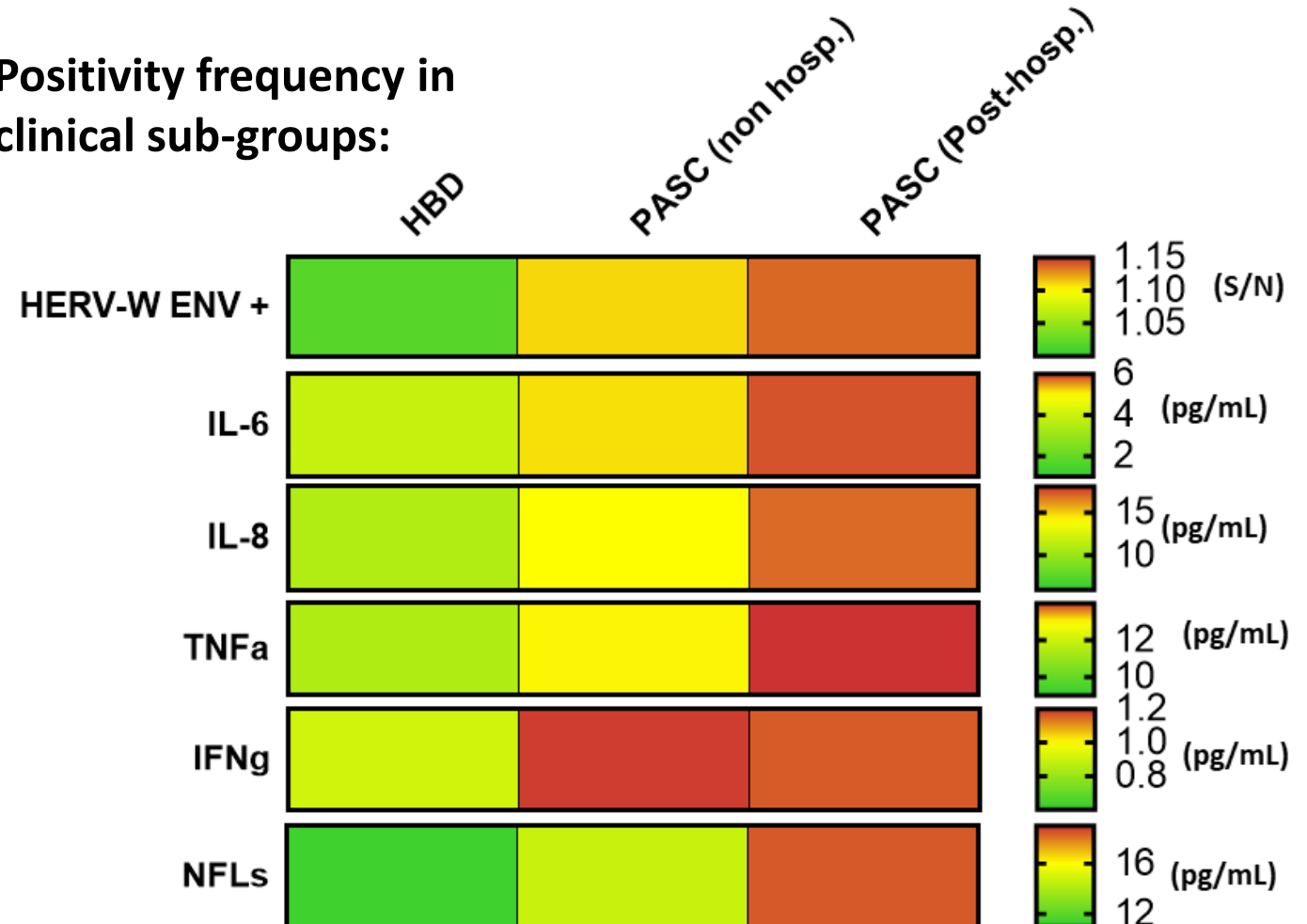
B. Ig anti-SARS-CoV-2 N-

1. Ig anti-SARS-CoV-2 N+ / HERV-W ENV+ /
IL6+ / TNF- α + / NfL+ /

2. Ig anti-SARS-CoV-2 N+ / HERV-W ENV- /
TNF- α - / NfL- / **IFN γ** +

3. Ig anti-SARS-CoV-2 N- / HERV-W ENV- / etc.

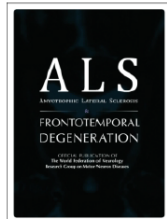
Positivity frequency in
clinical sub-groups:



HERV-K Env in sporadic ALS patients

Envelope protein detection in CSF

Neurotoxicity neutralized by specific antibody



Amyotrophic Lateral Sclerosis



ISSN: 1748-2968 (Print) 1471-180X (Online) Journal homepage: <http://www.tandfonline.com/loi/iafd19>

2009 Cerebrospinal fluid detection of enterovirus genome in ALS: A study of 242 patients and 354 controls

Nadia Vandenberghe, Nicolas Leveque, Philippe Corcia, Véronique Brunaud-Danel, Emmanuelle Salort-Campana, Gérard Besson, Christine Tranchant, Pierre Clavelou, Frédérique Beaulieux, René Ecochard, Christophe Vial, Emmanuel Broussolle & Bruno Lina

Neurotropic enterovirus(es)



HERV-K abnormal activation in CNS



Research Article | [Open Access](#) | | | | | 2022

Human Endogenous Retrovirus K Envelope in Spinal Fluid of Amyotrophic Lateral Sclerosis Is Toxic

Joseph P. Steiner PhD, Muzna Bachani BS, Nasir Malik PhD, Catherine DeMarino PhD, Wenxue Li PhD, Kevon Sampson MS, Myoung-Hwa Lee PhD, Jeffery Kowalak PhD ... [See all authors](#) ▾

First published: 08 July 2022 | <https://doi.org/10.1002/ana.26452> | Citations: 1

Acknowledgements



Plan-Les-Ouates, Genève, SWITZERLAND

Geneuro-Innovation SAS-Lyon, FRANCE

Benjamin Charvet, Joanna Brunel, Justine Pierquin, Nelly Queruel



Rome, ITALY

Claudia Matteucci, Emanuela Balestrieri, Antonella Minutolo, Vita Petrone, Marialaura Fanelli, Marco Iannetta, Vincenzo Malagnino, Marta Zordan, Pietro Vitale, Sergio Bernardini, Enrico Garaci, Loredana Sarmati, Sandro Grelli, Massimo Andreoni



Düsseldorf, University Hospital, GERMANY

Patrick Küry, David Kremer, Joel Gruchot



Lyon, INSERM U111, FRANCE

Said Mougari, Mathieu Lampietro, Didier Decimo, Cyrille Mathieu, Branka Horvat



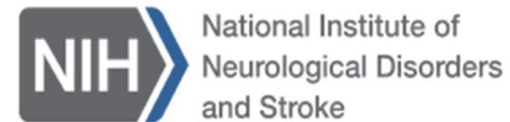
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Chicago, Northwestern University, USA

Jenine Ideis, Zachary Steven Orban, Igor Koralnik



Bethesda, MD, USA

Myoungwha Lee
Avindra Nath



Valencia, Spain

Karen Giménez-Orenga , Elisa Oltra-Garcia



Funded by
the European Union

HERVCOV

“SARS-CoV-2-induced activation of pathogenic endogenous retrovirus envelope HERV-W: towards personalized treatment of COVID-19 patients”



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