The Role of Viruses in Parkinson's Disease

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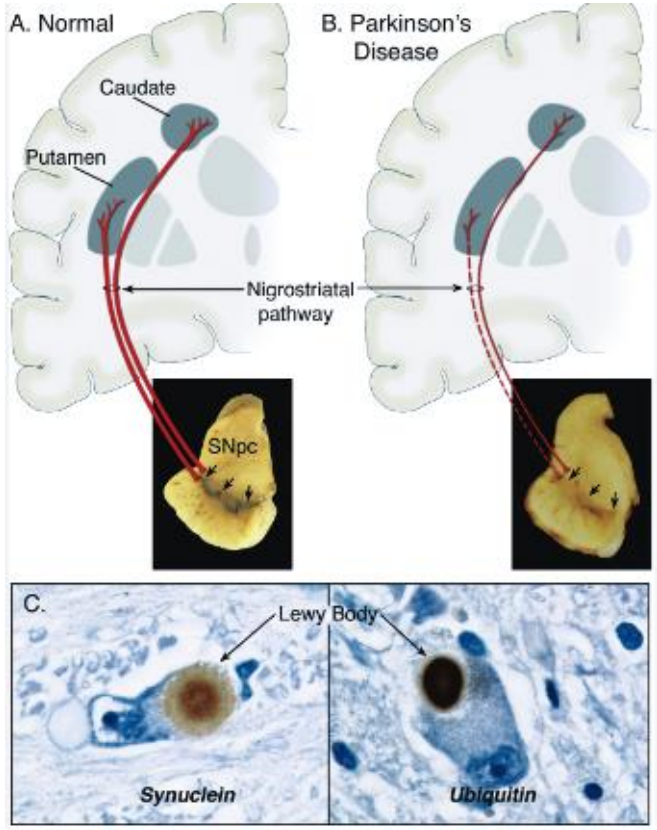
Overview of Parkinson's Disease (PD)

Clinical presentation, Epidemiology, Genetics and Pathophysiology

- Tremor, rigidity, slowness of movement, shuffling gait and stooped posture
- Affects 1.1 M people in the US and 10 M worldwide
- 1% people>60, 4%>80, Male/Female 1.5:1
- 10% genetic mutations
- Degeneration of dopaminergic neurons in brainstem substantia nigra
- Caused by α-synuclein misfolding, accumulation of Lewy bodies and prion-like propagation hypothesis



Dauer Neuron 2003

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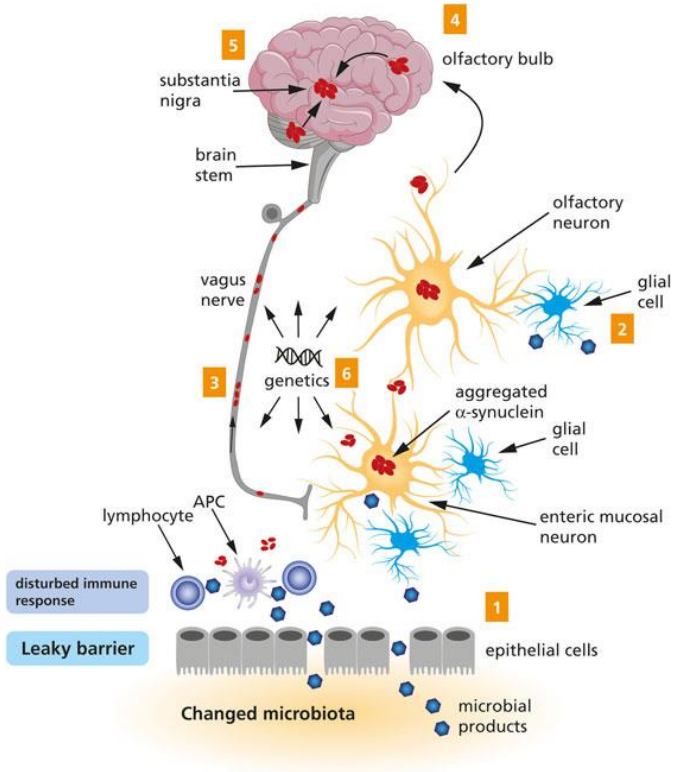
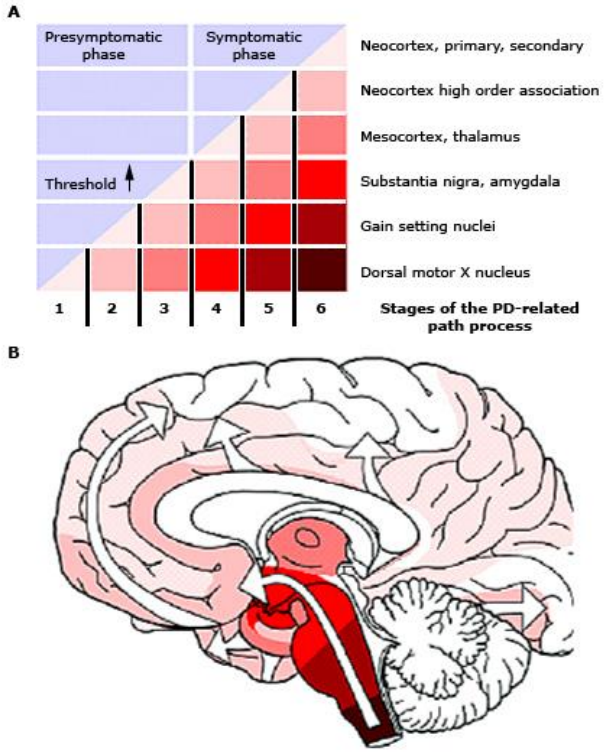
Parkinson's Disease occurs in the gut and nasopharynx before progressing into the CNS

- Potential ports of entry of viruses into the CNS via the Vagus Nerve and olfactory mucosa



Rietdijk Front Neurol 2017



Braak Cell Tissue Res 2004

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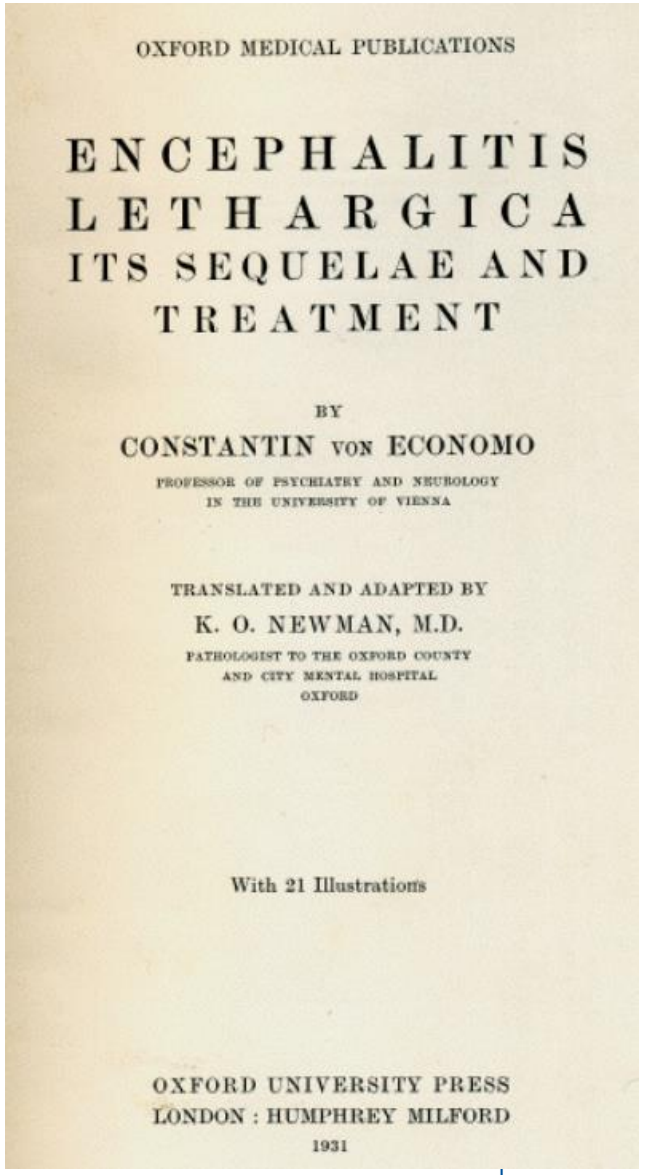
Parkinsonism in viral/post-viral encephalitis

- Encephalitis lethargica affecting ~1 M people 1915-1926
- Mortality ~10-50%
  - Variable by wave and severity
- Parkinsonism occurring during or after encephalitis
- Virus suspected but never proven
- Can be treated with Dopamine
  Bigman Neuropsychiatr Dis Trea 2018


OXFORD MEDICAL PUBLICATIONS

ENCEPHALITIS LETHARGICA
ITS SEQUELAE AND TREATMENT

BY
CONSTANTIN von ECONOMO
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TRANSLATED AND ADAPTED BY
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With 21 Illustrations

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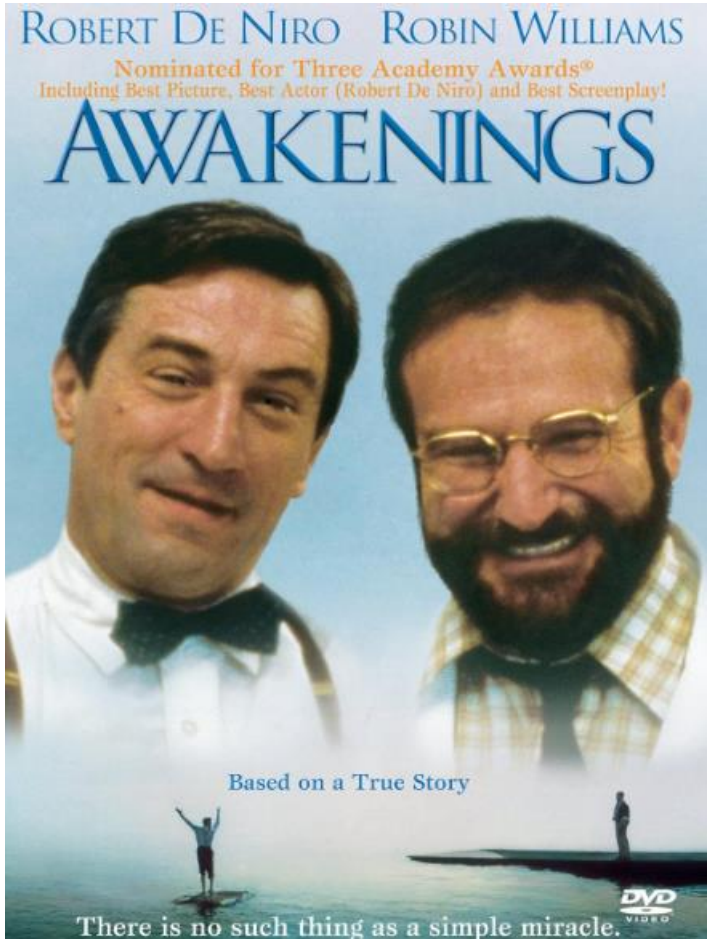

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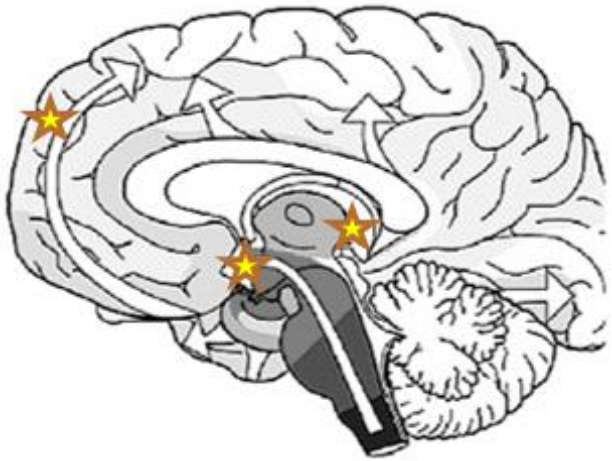
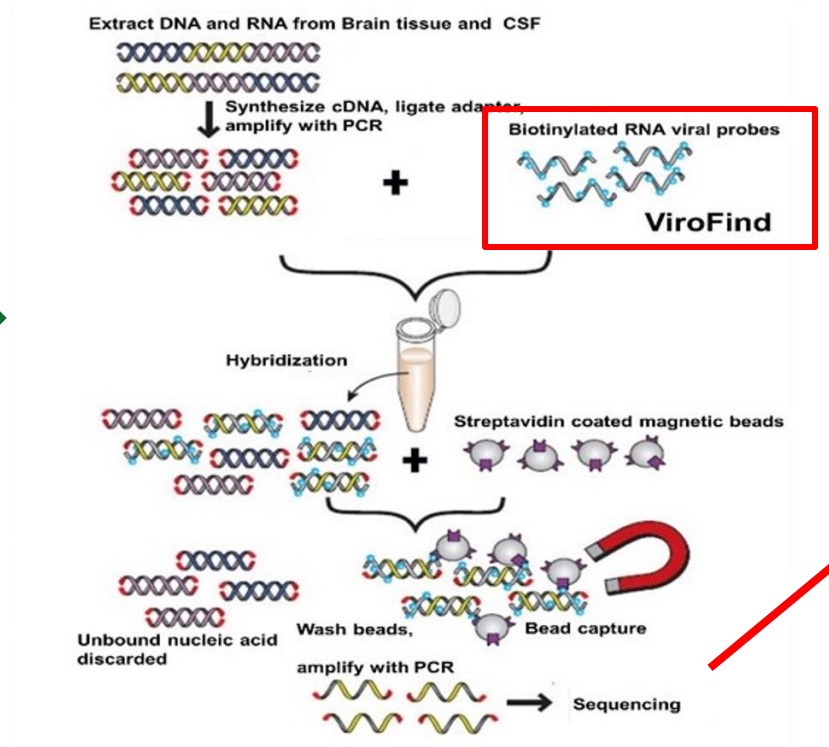
Characterizing the PD brain virome with ViroFind

A target-enrichment, deep sequencing platform for virus detection and discovery in clinical samples



Fresh frozen post-mortem PD and control samples:

- **Amygdala**
- **Posterior putamen**
- **Superior frontal cortex**



- **565 selected DNA or RNA viruses that can infect humans or cause zoonosis**
- **131,706 viral probes (8.415 Mbp) with mean coverage of 89.4% viral genomes**
- **Potential to detect virus variants and yet undiscovered viruses**

Bioinformatics Pipeline
Detection / Variants / Integration

Enrichment of Viral sequences up to 127 fold compared to metagenomic Next Gen sequencing Chalkias PLOS ONE 2018

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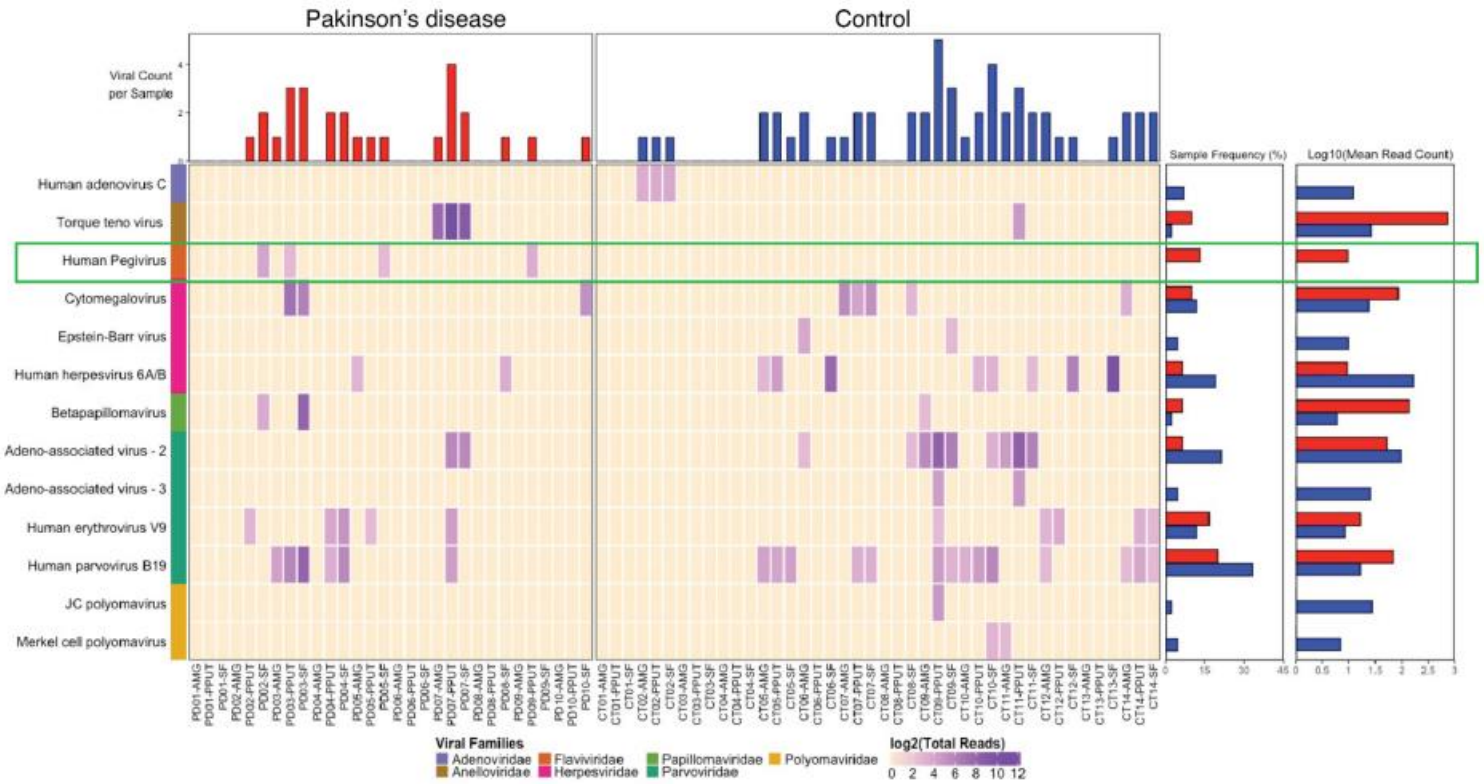
Discovery of Human Pegivirus in PD brain samples Hanson JCI Insight 2025



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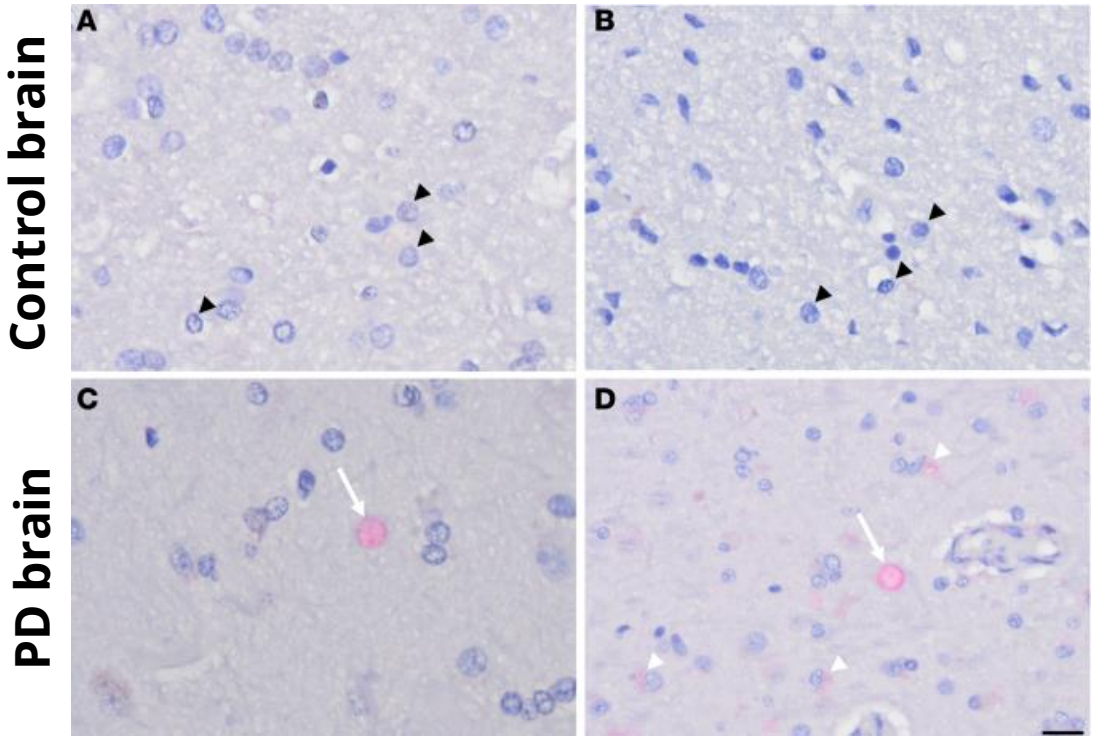
Human Pegivirus (HPgV) detection in PD brain and CSF but not in control samples

Table 3. Detection of HPgV in brain and bodily fluids of PD and controls.

	Amygdala		Posterior putamen		Superior frontal Cx		Total brain regions			CSF	Plasma
	ViroFind	qPCR	ViroFind	qPCR	ViroFind	qPCR	ViroFind	qPCR	Summary	qPCR	qPCR
PD01	-	-	-	-	-	-	0	0	-	-	-
PD02	-	+	-	-	+	+	1	2	Pos	-	-
PD03	-	-	+	+	-	-	1	1	Pos	+	-
PD04	-	-	-	+	-	-	0	1	Pos	-	-
PD05	-	+	-	+	+	+	1	3	Pos	+	-
PD06	-	-	-	-	-	-	0	0	-	-	-
PD07	-	-	-	-	-	-	0	0	-	-	-
PD08	-	-	-	-	-	-	0	0	-	-	-
PD09	-	+	+	+	-	+	1	3	Pos	+	-
PD10	-	-	-	-	-	-	0	0	-	-	-
	0/10	3/10	2/10	4/10	2/10	3/10	4/10	10/30	5/10	3/10	0/10
CT01	-	-	-	-	-	-	0	0	-	-	-
CT02	-	-	-	-	-	-	0	0	-	-	-
CT03	-	-	-	-	-	-	0	0	-	-	-
CT04	-	-	-	-	-	-	0	0	-	-	-
CT05	-	-	-	-	-	-	0	0	-	-	-
CT06	-	-	-	-	-	-	0	0	-	-	-
CT07	-	-	-	-	-	-	0	0	-	-	-
CT08	-	-	-	-	-	-	0	0	-	-	-
CT09	-	-	-	-	-	-	0	0	-	-	-
CT10	-	-	-	-	-	-	0	0	-	-	-
CT11	-	-	-	-	-	-	0	0	-	-	-
CT12	-	-	-	-	-	-	0	0	-	-	-
	0/12	0/12	0/12	0/12	0/12	0/12	0/36	0/36	0/12	0/12	0/12

PD, Parkinson's disease; CT, control; Cx, cortex; Pos, positive detection.



HPgV NS5A positive oligodendrocytes in subcortical white matter of 2 PD cases

- **HPgV-positive PD patients:**
  - Advanced neurofibrillary tangle pathology in limbic area (Braak staging)
  - Higher Complexin-II levels, suggesting enhanced glutamate release (exitotoxicity)

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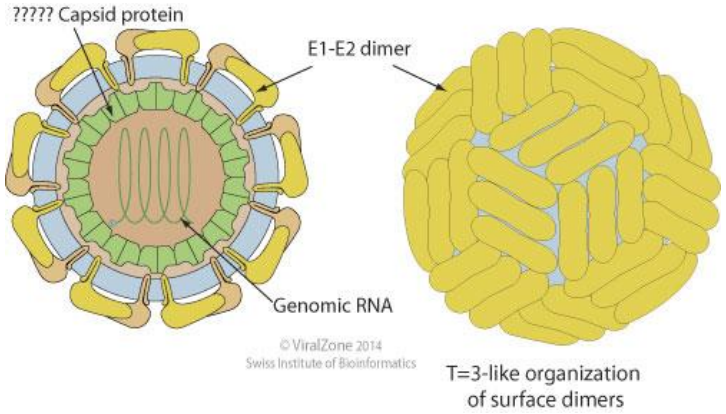
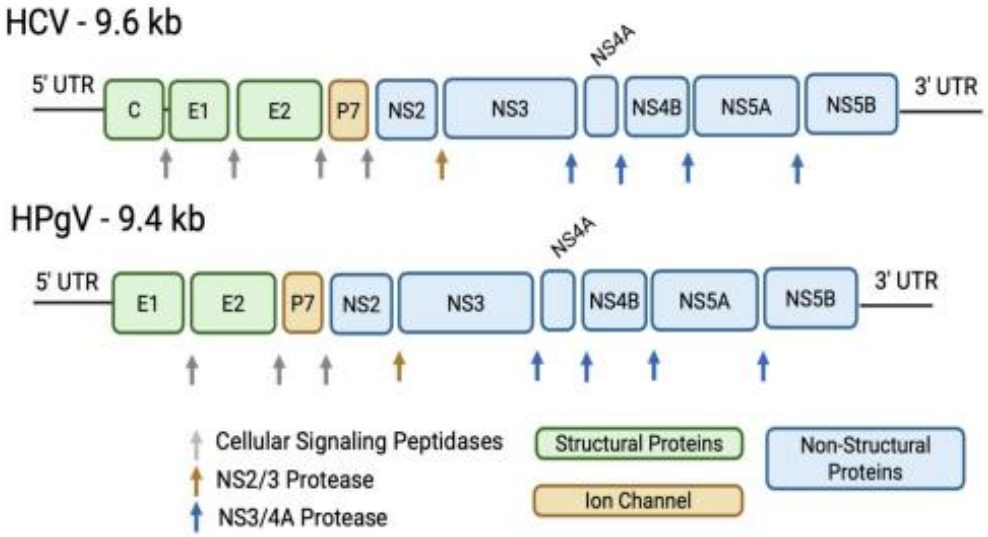
Human Pegivirus (HPgV)

- Previous names: Hepatitis G virus, GB virus C
- Pan-lymphotropic + sense, single strand RNA Flavivirus
- Similar genome organization to Hepatitis C virus without a capsid gene
- Subclinical infection / understudied-resourced
- Persistent viremia over years/decades in 1-5% healthy blood donors (up to 40% in HIV+)
- Persistence through dampening immune activation **Chivero Virology 2015**
- Beneficial in HIV and Ebola infection:
  - Increase CD4+ T cells, reduce mortality 2.5x **Tillman NEJM 2001, Lauck J Virol 2015, Yu Virulence 2022**
  - Interferes with TCR signaling by reducing proximal activation of the lymphocyte-specific Src kinase LCK **Stapleton Front Immunol 2022**
  - **Immunomodulation without suppression: "biotherapeutic ?"**
- Rare cases of acute brain infection **Balcom Ann Neurol 2018**





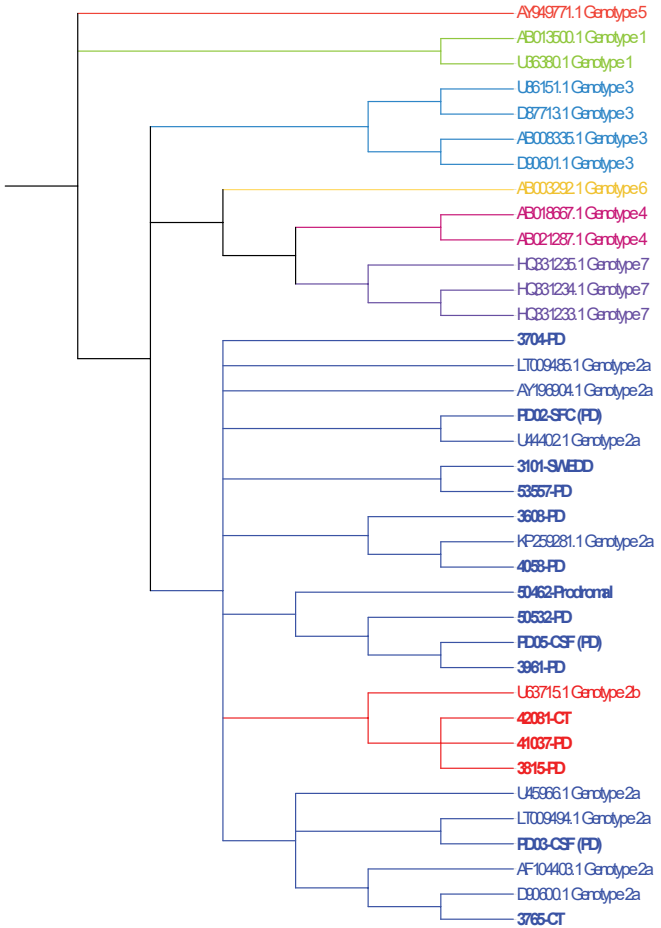
HPgV and other viruses in whole blood transcriptome of PD patients, prodromal cases and controls (n=1393)

Mining the database of the Parkinson Progression Markers Initiative (PPMI)

Table 5. ViroFind results from whole-blood of PPMI participants.

		PD	Prodromal	SWEDD	CT	*P* value
		(*n* = 753)	(*n* = 287)	(*n* = 54)	(*n* = 299)	
Age	mean [SD]	63.66	63.16	62.14	62.16	0.128
Sex	*n* (%)					
F		320 (42)	146 (51)	20 (37)	140 (47)	0.053
M		433 (58)	141 (49)	34 (63)	159 (53)	
Race	*n* (%)					
Asian		10 (1)	0 (0)	1 (2)	2 (1)	0.726
Black		7 (1)	1 (0)	1 (2)	5 (2)	
White		728 (96)	282 (99)	51 (94)	291 (96)	
Indigenous North American		4 (1)	1 (0)	0 (0)	2 (1)	
Pacific Islander		1 (0)	0 (0)	0 (0)	0 (0)	
Unspecified		10 (1)	0 (0)	1 (2)	2 (1)	
Ethnicity	*n* (%)					
Hispanic		60 (8)	40 (14)	2 (4)	21 (7)	0.005
Non-Hispanic		693 (92)	247 (86)	52 (96)	277 (93)	
Genetic cohort	*n* (%)	517	130	54	165	
GBA		69 (13)	18 (14)	3 (6)	8 (5)	0.009
LRRK2		228 (44)	77 (59)	16 (30)	41 (25)	<0.001
SNCA		12 (2)	4 (3)	0 (0)	0 (0)	0.119
Adenoviridae						
Human adenovirus C	*n* (%)	247 (32.8)	116 (40.4)	14 (25.9)	114 (38.1)	0.037
	M rPM(IQR)	0.22 (0.14–0.41)	0.25 (0.15–0.44)	0.16 (0.15–0.25)	0.27 (0.17–0.36)	0.151
Herpesviridae						
EBV	*n* (%)	48 (6.4)	12 (4.2)	2 (3.7)	28 (9.4)	0.062
	M rPM(IQR)	0.18 (0.14–0.59)	0.16 (0.14–0.28)	0.14 (0.14–0.14)	0.58 (0.21–3.32)	0.022
HHV6A/B	*n* (%)	6 (0.8)	1 (0.3)	0 (0)	1 (0.3)	0.677
	M rPM(IQR)	4.40 (0.75–13.76)	0.25 (NA)	NA (NA)	0.20 (NA)	0.130
HHV7	*n* (%)	20 (2.7)	5 (1.7)	0 (0)	8 (2.7)	0.534
	M rPM(IQR)	0.11 (0.07–0.13)	0.11 (0.06–0.12)	NA (NA)	0.07 (0.07–0.08)	0.391
Flaviviridae						
Human Pegivirus C	*n* (%)	8 (1.1)	1 (0.3)	2 (3.7)	3 (1.0)	0.156
	M rPM(IQR)	43.09 (20.98–66.45)	54.91 (NA)	59.51 (29.85–89.18)	22.83 (11.44–39.02)	0.774
Hepatitis C virus	*n* (%)	1 (0.1)	1 (0.3)	0 (0)	1 (0.3)	0.852
	M rPM(IQR)	3.05 (NA)	4.07 (NA)	NA (NA)	3.19 (NA)	NA
Papillomaviridae						
Human papilloma virus spp.	*n* (%)	11 (0.15)	2 (0.7)	1 (1.9)	3 (1)	0.727
	M rPM(IQR)	0.15 (0.13–0.16)	0.26 (0.21–0.31)	0.14 (NA)	0.20 (0.18–0.23)	0.229
Anelloviridae						
Torque teno virus spp.	*n* (%)	15 (2)	4 (1.4)	1 (1.9)	1 (0.3)	0.258
	M rPM(IQR)	0.14 (0.13–0.29)	0.09 (0.07–0.12)	0.15 (NA)	0.06 (NA)	0.128

M rPM, median reads per million; HHV, human herpesvirus; spp., species; PD, Parkinson's disease; SWEDD, scans without evidence of dopamine deficiency; CT, non-PD controls.



- **Prevalence:** no difference of HPgV or other viruses in blood of PD and controls
- **Phylogenetic analysis:** HPgV genotype 2a or 2b (Europe and Americas)
- **Sequence alignment:** no PD-associated HPgV variants in brain, CSF or blood.

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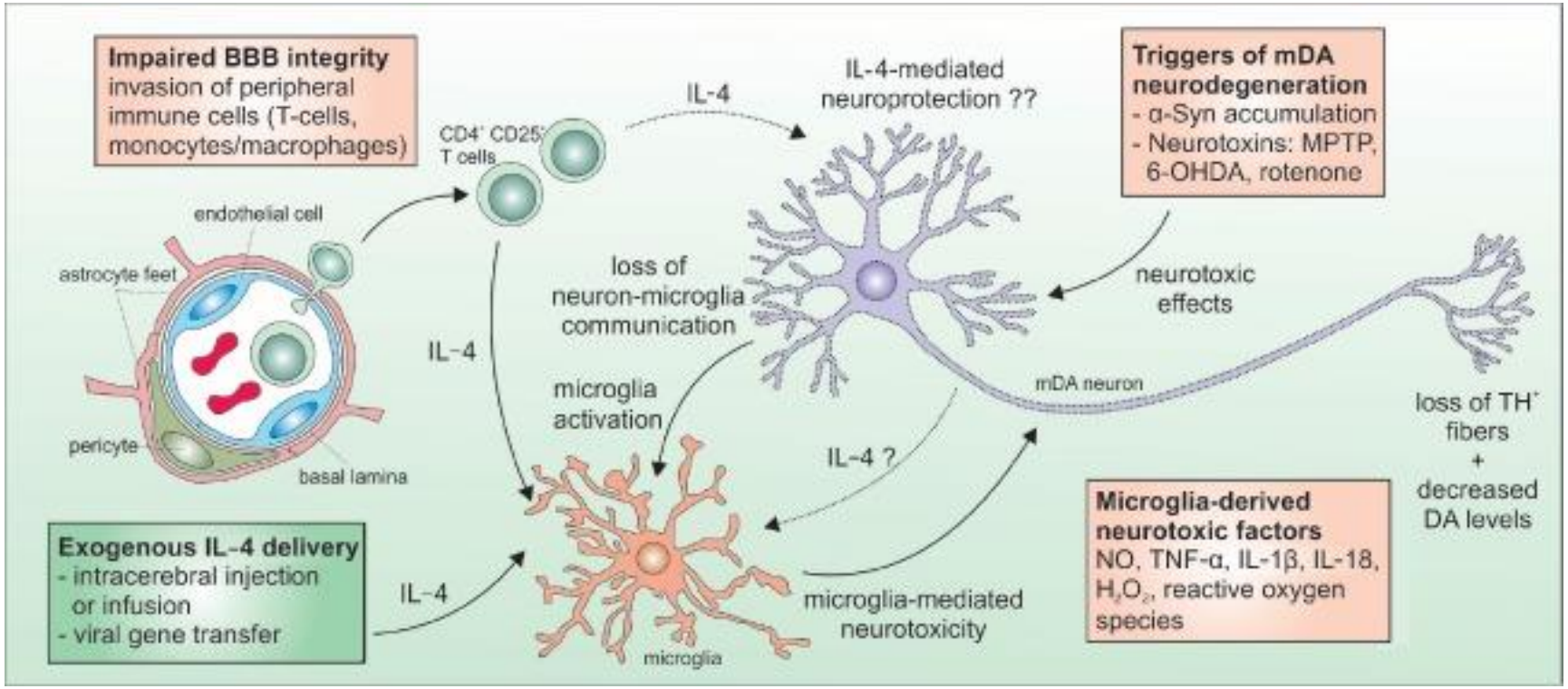
IL-4 signaling is altered in HPgV+ PD

- IL-4 promotes a protective anti-inflammatory response in the brain
  - pushes microglia toward an M2-like/homeostatic state
  - supports neuronal survival and helps dampen chronic neuroinflammation
- HPgV-positive PD brains:
  - local suppression of IL-4 signaling
  - Microglia remain in a chronically activated, pro-inflammatory state.
- Acceleration of dopaminergic neuron vulnerability and synuclein-related pathology
- Worsening Parkinson's disease progression through increased neuroinflammation



Spittau Neural Regen Res. 2017

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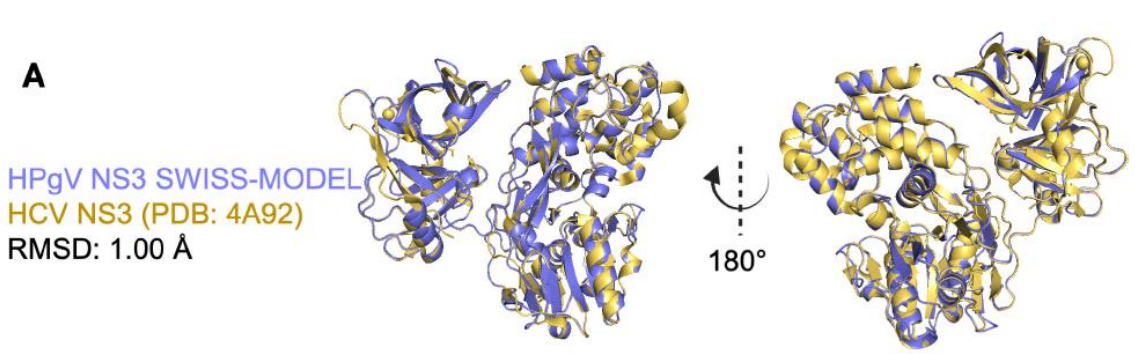
Repurposing anti-HCV drugs against HPgV?

- HCV and HPgV infections often coexist **Ng Sci Rep 2015**
- Association of HCV infection and PD **Tsai Neurol 2016**
- Decreased risk of PD in Hepatitis C patients treated with anti-HCV medications **Lin JAMA Neurol 2019**
- HCV not found in brains of PD: associations caused by HPgV coinfection?
- **Hypothesis:**
  - **anti-HCV medications could be active against HPgV**

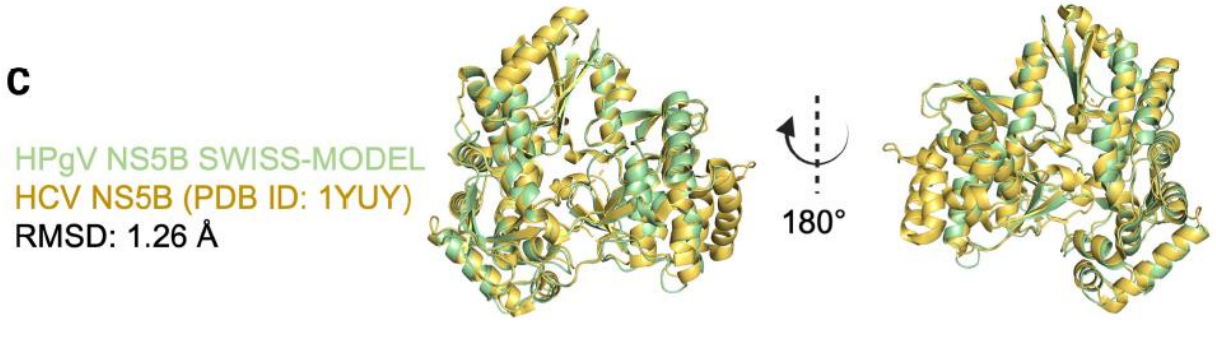
In-silico modeling of anti-HCV drugs docking to HPgV NS3 and NS5B proteins Copenhaver Viruses 2026

Table 1. FDA-Approved HCV direct-acting antivirals.

Trade Name	Small Molecule Combinations	HCV Protein Target(s)		
		NS3	NS5A	NS5B
Harvoni	Ledipasvir/Sofosbuvir		X	X
Zepatier	Grazoprevir/Elbasvir	X	X	
Epclusa	Velpatasvir/Sofosbuvir		X	X
Vosevi	Voxilaprevir/Velpatasvir/Sofosbuvir	X	X	X
Mavyret	Glecaprevir/Pibrentasvir	X	X	



NS3: 43% aa identity and 55% similarity



NS5B: 34% aa identity and 50% similarity

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Similar predicted docking affinity of antivirals to HCV and HPgV NS3 and NS5B proteins

Drug	HCV Protein Target	Docking Affinity (kcal/mol)		
		HPgV NS3/4A SWISS-MODEL	HPgV NS3/4A AlphaFold Model	HCV NS3/4A (PDB ID: 4A92)
Glecaprevir	NS3/4A	−11.5	−8.9	−12.5
Paritaprevir	NS3/4A	−11.4	−8.6	−12.4
Simeprevir	NS3/4A	−10.7	−8.6	−11.8
Voxilaprevir	NS3/4A	−10.6	−8.9	−11.8
Grazoprevir	NS3/4A	−9.8	−7.6	−11.1
Telaprevir	NS3/4A	−7.6	−6.2	−8.4
Boceprevir	NS3/4A	−7.4	−6.3	−7.5

Drug	HCV Protein Target	Docking Affinity (kcal/mol)		
		HPgV NS5B SWISS-MODEL	HPgV NS5B AlphaFold Model	HCV NS5B (PDB ID: 1YUY)
Dasabuvir	NS5B	−8.5	−8.3	−11.5
Sofosbuvir	NS5B	−7.2	−7.0	−7.5

- decreased HPgV viremia in Hepatitis C patients treated with anti-HCV medications **Hlavay J Clin Virol 2023**

Conclusions

- HPgV identified in 50% of post-mortem PD brains and 30% of PD CSF samples in a pilot study using unbiased ViroFind platform
- HPgV is associated with advanced brain pathology
- HPgV suppresses IL-4 signaling in PD patients which may contribute to PD pathogenesis
- **We do not claim that HPgV causes PD!**
- High similarity between HPgV and HCV NS3 and NS5B proteins
- In-silico modeling suggest that HCV antivirals will also be active against HPgV

Next Steps:

- Collaboration with PD experts from Sidney Brain Bank, Australia
  - Testing post-mortem brains from 30 PD and 20 age/sex matched controls
  - Molecular and histological analyses
- Looking for positive control for HPgV IHC: human appendix samples
  - Appendicectomy reduces the risk of PD by 20%. **Killinger Science Translat Med 2018**
- Applying for presymptomatic CSF and blood samples for HPgV testing: REM-sleep behavior disorder cohort
- Mining databases for incidence of Hepatitis C treatment in people with PD and effect on outcome
- Ongoing discussion with Gilead Sciences
- Open to new ideas and collaborations!

Thank You!

Collaborators

- Barbara Hanson
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- Kaleigh Copenhaver
- Zack Orban
- Bernabe Bustos
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- Rudi Castellani
- Steven Lubbe
- Joshua Ziarek

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