Interrogating the role of the brain virome in Alzheimer’s Disease

Ben Readhead M.B.B.S.  
19th July 2018
Outline

• Network biology of “preclinical AD” suggests viral influence
• Multiomic evaluation of brain virome in AD
• Evidence for leading role of herpesviridae
Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Ben Readhead,1,2,3,4,17 Jean-Vianney Haure-Mirande,5,17 Cory C. Funk,6 Matthew A. Richards,6 Paul Shannon,6 Vahram Haroutunian,7,8 Mary Sano,6,15 Winnie S. Liang,9,10 Noam D. Beckmann,1,2 Nathan D. Price,6 Eric M. Reiman,9,10,11,12 Eric E. Schadt,1,2,13 Michelle E. Ehrlich,1,2,5,14 Sam Gandy,5,8,15,16,17 and Joel T. Dudley1,2,3,4,17,18,*

1Departments of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
2Icahn Institute of Genomic Sciences and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
3Institute for Next Generation Healthcare, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
4ASU-Banner Neurodegenerative Disease Research Center, Arizona State University, Tempe, AZ 85287-5001, USA
5Department of Neurology, Alzheimer’s Disease Research Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
6Institute for Systems Biology, Seattle, WA, 98109-5263, USA
7Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
8James J. Peters VA Medical Center, 130 West Kingsbridge Road, New York, NY 10468, USA
9Arizona Alzheimer’s Consortium, Phoenix, AZ 85014, USA
10Neurogenomics Division, Translational Genomics Research Institute, Phoenix, AZ 85004, USA
11Department of Psychiatry, University of Arizona, Phoenix, AZ 85721, USA
12Banner Alzheimer’s Institute, Phoenix, AZ 85006, USA
13Sema4, Stamford, CT 06902, USA
14Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
15Department of Psychiatry, Alzheimer’s Disease Research Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
16Center for NFL Neurological Care, Department of Neurology, New York, NY 10029, USA
17These authors contributed equally
18Lead Contact

*Correspondence: joel.dudley@mssm.edu
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Alzheimer’s Disease

Parkinson’s Disease

Niemann-Pick C

Dystonia

Huntington’s Disease

Neuroplasticity

Asthma

Coronary Artery Disease

Pulmonary Fibrosis

Noonan’s Syndrome

Skin atrophy

Non-alcoholic steatohepatitis

Cystic Fibrosis

Hepatic Fibrosis

Acne

Renal Fibrosis

Multiple Myeloma

Ovarian Cancer

Ebola Virus Disease

Prostate Cancer

Efforts in drug repurposing
Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer’s Disease

Bin Zhang,1,2,3,4,14, Chris Gaitheri,4,14 Liviu-Gabriel Bodea,5,14 Zhi Wang,4 Joshua McElwee,6 Alexei A. Podtelezhnikov,7 Chunsheng Zhang,6 Tao Xie,6 Linh Tran,4 Radu Dobrin,6 Eugene Fluder,6 Bruce Clurman,6 Stacey Melquist,6 Manikandan Narayanan,8 Christine Suver,4 Hardik Shah,1,2 Milind Mahajan,1,2,3 Tammy Gillis,9 Jayalakshmi Mysore,9 Marcy E. MacDonald,9 John R. Lamb,10 David A. Bennett,11 Cliona Molony,6 David J. Stone,7 Vilmundur Gudnason,12 Amanda J. Myers,13 Eric E. Schadt,1,2,3 Harald Neumann,5 Jun Zhu,1,2,3 and Valur Emilsson12,*

Exploring the network biology of “preclinical AD”

Healthy network

Vs.

Preclinical AD network

CA1 Hippocampus + Entorhinal Cortex


Multiomic evaluation of Alzheimer’s Disease associated virome

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
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Multiomic evaluation of Alzheimer’s Disease associated virome

Hippocampal - Entorhinal Cortex
Gene regulatory network

Preclinical Vs. Controls

Viral themes
- Viral enrichments in network drivers
- Shift in C2H2 zinc finger networks
- Altered G-quadruplex activity
- Integrative analysis (e.g. SP1, mir-155)

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**Causal network inference**

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**Multidomain viral summary**
**Differential abundance of viral RNA in AD**

### a. Viral RNA Level

<table>
<thead>
<tr>
<th>Virus Level</th>
<th>Anterior Prefrontal Cortex</th>
<th>Superior Temporal Gyrus</th>
<th>Parahippocampal Gyrus</th>
<th>Inferior Frontal Gyrus</th>
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<tbody>
<tr>
<td>HHV-6A</td>
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### b. Virus Gene Level

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<tr>
<th>Virus Gene Level</th>
<th>AD Definite</th>
<th>AD Likely</th>
<th>AD Possible</th>
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<th>AD Possible</th>
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Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
### Differential abundance of viral RNA in AD

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<thead>
<tr>
<th>Virus level</th>
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<td>1.2e-02</td>
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<tr>
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</tbody>
</table>

#### Virus gene level

| Virus | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible | AD Definite | AD Likely | AD Possible |
|-------|-------------|------------|-------------|-------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-------------|-------------|------------|-------------|-------------|------------|-------------|-------------|------------|-------------|
| HHV-6A| 1.4e-05     | 1.2e-09    |             | 1.1e-03     |            |             |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |
| HHV-7 | 1.0e-09     | 2.0e-10    |             | 8.1e-04     | 4.6e-03    |             |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |
| HSV-2 | 3.7e-06     | 1.0e-03    | 3.0e-03     |             | 3.5e-10    | 3.2e-03     |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |
| HSV-1 | 2.6e-05     | 2.1e-07    | 1.6e-04     |             |            |             |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |
| KSHV  | 4.7e-06     | 4.3e-05    | 1.1e-06     |             |            |             |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |
| HAdV-B1| 2.6e-03    | 1.5e-12    | 2.8e-16     |             |            |             |             |             |             |             |             |            |             |             |            |             |             |             |             |             |             |

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Differential abundance of viral DNA in AD

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Differential abundance of viral DNA in AD

Differential DNA abundance

Signed -log10(P-Value)

Viral DNA

Superior Temporal Gyrus

HHV-6A

HHV-6B

AD Definite

AD Likely

AD Possible

Virus level

Virus gene level

HHV-6A

 HSV-2

 HSV-1

 KSHV

Region 8009 -151234

Region 133709 - 148033

Region 9301 - 118020

Repeat region 118021 - 127320

Region 140291 - 143588

LAT 7065 -7767

LAT 119554 - 127991

LAT 1 - 7814

LAT 118777 -127151

Repeat region 23082 -24228

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Meta-analysis of differential abundance of viral RNA in AD

**Viral RNA**

A

<table>
<thead>
<tr>
<th>Mount Sinai Brain Bank</th>
<th>Religious Orders Study</th>
<th>Memory &amp; Aging Project</th>
<th>MAYO TCX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Prefrontal Cortex</td>
<td>Superior Temporal Gyrus</td>
<td>Ectorial Cortex</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>n=213</td>
<td>n=96</td>
<td>n=107</td>
<td>n=186</td>
</tr>
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<td>6.9e−10</td>
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<td>1.4e−02</td>
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<tr>
<td>2.7e−08</td>
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</table>

**Meta-analysis P-Value**

HHV-6A

HHV-7

**Meta-analysis P-Value**

U3 / U4 gene

Region 8009 - 151234

Region 10035 - 143046

Repeat region 118021 - 127320

Repeat region 1 - 9300

Gene 1 - 7569 LAT

Repeat region 23082 - 24228

Repeat region 24823 - 25045

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<tbody>
<tr>
<td></td>
<td>n=213</td>
<td>n=107</td>
<td>n=247</td>
<td>n=232</td>
</tr>
<tr>
<td></td>
<td>Anterior Prefrontal Cortex</td>
<td>Ectorhinal Cortex</td>
<td>Inferior Frontal Gyrus</td>
<td>Dorsolateral Prefrontal Cortex</td>
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<tr>
<td></td>
<td>Superior Temporal Gyrus</td>
<td>n=96</td>
<td>n=186</td>
<td>n=247</td>
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<tr>
<td></td>
<td>AD Possible vs Control</td>
<td>AD Possible vs Control</td>
<td>AD Possible vs Control</td>
<td>AD Possible vs Control</td>
</tr>
</tbody>
</table>

**P-Value**
- Religious Orders Study: 6.9e-10, 2.6e-02, 2.7e-08, 4.2e-04
- Memory & Aging Project: 1.2e-09, 5.0e-10, 1.6e-04, 2.0e-04
- MAYO TCX: 1.2e-09, 2.8e-16, 6.2e-03, 1.2e-16, 6.2e-03, 1.2e-04, 1.1e-05

**Differential RNA abundance**
- Range: -15 to 15

**Virus level**
- HHV-6A: 1.2e-09, 2.0e-10
- HHV-7: 5.0e-10
- HSV-2: 1.6e-04, 2.0e-04
- HSV-1: 4.1e-08, 1.6e-03, 4.0e-06, 1.2e-05, 1.1e-02
- KSHV: 2.8e-16, 6.2e-03, 7.1e-09, 1.2e-04, 1.1e-05

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### Viral RNA

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<td>Inferior Frontal Gyrus</td>
<td>186</td>
<td>Dorsolateral Prefrontal Cortex</td>
<td>n=247</td>
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</table>

#### Meta-analysis P-Value

- **HHV-6A**: Meta-analysis P-Value
  - AD Possible vs. Control: 1.2e-09
  - AD Possible vs. Control: 2.0e-10

#### Virus level

- **HHV-6A**: Meta-analysis P-Value
  - AD Possible vs. Control: 1.2e-09
  - AD Possible vs. Control: 2.0e-10

#### Virus gene level

- **HHV-6A**: Meta-analysis P-Value
  - U3 / U4 gene: 1.0e-07
  - Region 8009 - 151234: 1.7e-03
  - Region 10035 - 143046: 2.4e-10
  - Repeat region 118021 - 127320: 1.2e-03
  - Repeat region 1 - 9300: 1.2e-03
  - Repeat region 23082 - 24228: 7.1e-09
  - Repeat region 24823 - 25045: 1.1e-05

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Meta-analysis of differential abundance of viral RNA in AD

**Viral RNA**

<table>
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<tr>
<th>Virus</th>
<th>AD Possible vs Control</th>
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</table>

**Virus level**

- HHV-6A: Meta-analysis P-Value = 1.2e-03
- HHV-7: Meta-analysis P-Value = 1.2e-03

**Differential RNA abundance**

- HHV-6A: 5.5e-07
- HHV-7: 3.7e-05

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
Viral abundance correlates with AD associated clinical and neuropathology traits

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Detecting viral quantitative trait loci (vQTL)

\[ \text{Viral abundance} \sim \text{DNA Marker} + \text{Sex} + \text{Ethnicity} + \text{Age} + \text{Batch} + \text{RIN} + \text{PMI} \]

vQTL comparison with cis-eQTL

vQTL associations with AD traits

Causal inference of virus-host networks

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
### Top multi-virus vQTL

<table>
<thead>
<tr>
<th>vQTL</th>
<th>Chr</th>
<th>Pos</th>
<th>Overlapping Gene</th>
<th>Name</th>
<th>Region</th>
<th>Viruses</th>
<th># Viral genes</th>
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<tr>
<td>rs71454075</td>
<td>11</td>
<td>1018138</td>
<td>MUC6</td>
<td>Mucin 6, oligomeric mucus/gel-forming</td>
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<td>HAdV-C, HSV-2, Variola</td>
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<td>rs62229372</td>
<td>21</td>
<td>37692507</td>
<td>MORC3</td>
<td>MORC Family CW-Type Zinc Finger 3</td>
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<td>rs41267413</td>
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<td>Interferon Stimulated Exonuclease Gene 20 Like 2</td>
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<td>167085079</td>
<td>SCN9A</td>
<td>Sodium Voltage-Gated Channel Alpha Subunit 9</td>
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<tr>
<td>rs10839326</td>
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<td>rs2867972</td>
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<td>HSV-1</td>
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</tbody>
</table>
vQTL associate with AD status, clinical dementia and neuropathological features of AD

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
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Causal network inference
Using viral QTLs to build virus/host molecular, neuropathology and clinical networks

Causal network inference

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
### Detected Virus / Host interactions

<table>
<thead>
<tr>
<th>Virus</th>
<th>APFC</th>
<th>STG</th>
<th>PHG</th>
<th>IFG</th>
<th>Total</th>
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</thead>
<tbody>
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</table>

<table>
<thead>
<tr>
<th>Virus</th>
<th>APFC</th>
<th>STG</th>
<th>PHG</th>
<th>IFG</th>
<th>Total</th>
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<tr>
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<td>12</td>
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<td>22</td>
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</tbody>
</table>

- **Virus to Host**
- **Host to Virus**

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Frequently perturbed genes

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
<th>APFC</th>
<th>STG</th>
<th>ERC</th>
<th>IFG</th>
<th>Viruses</th>
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<td>✓</td>
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<tr>
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<tr>
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<td>HHV-6A, HSV-2, HCMV</td>
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<td>✓</td>
<td>✓</td>
<td>HHV-6A, HSV-1, HCMV</td>
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</tbody>
</table>

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<td>✓</td>
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<td>cysteinyltRNA synthetase</td>
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<td>FYN</td>
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<td>K(lysine) acetyltransferase 8</td>
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<td>MCAM</td>
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DOI 10.1038/s41398-018-0150-6

Translational Psychiatry

Symbol
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BACE1  beta-site Al
CARS  cysteiny1-tF
FYn  FYN proto-
K(lysine) a
KAT8  melanoma
MCAM  Macrophaç
MST1P9  NLR family
NLRC4  one cut hom
ONECUT2  protocadhe
PCGF6  polycomb f
PPARG  peroxisome
SIAE  sialic acid a
SRSF6  serine/argi

GWAS on family history of Alzheimer’s disease

Riccardo E. Marioni1,2, Sarah E. Harris1,2, Qian Zhang3, Allan F. McRae1,3, Saskia P. Hagaenaars2,4, W. David Hill2,5, Gail Davies2, Craig W. Ritchie6, Catharine R. Gale2,5,7, John M. Starr2,8, Alison M. Goate2,9, David J. Porteous1,2, Jian Yang3,10, Kathryn L. Evans1, Ian J. Deary2,5, Naomi R. Wray1,3,10 and Peter M. Visscher2,3,10

Abstract
Alzheimer’s disease (AD) is a public health priority for the 21st century. Risk reduction currently revolves around lifestyle changes with much research trying to elucidate the biological underpinnings. We show that self-report of parental history of Alzheimer’s dementia for case ascertainment in a genome-wide association study of 314,278 participants from UK Biobank (27,696 maternal cases, 14,338 paternal cases) is a valid proxy for an AD genetic study. After meta-analysing with published consortium data (n = 74,046 with 25,580 cases across the discovery and replication analyses), three new AD-associated loci (p < 5 × 10^-6) are identified. These contain genes relevant for AD and neurodegeneration: ADAM10, BCKD/KAT8 and ACE. Novel gene-based loci include drug targets such as VKOR1 (warfarin dose). We report evidence that the association of SNPs in the TOMM40 gene with AD is potentially mediated by both gene expression and DNA methylation in the prefrontal cortex. However, it is likely that multiple variants are affecting the trait and gene methylation/expression. Our discovered loci may help to elucidate the biological mechanisms underlying AD and, as they contain genes that are drug targets for other diseases and disorders, warrant further exploration for potential precision medicine applications.

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Viral regulation of AD associated host networks
Viral regulation of AD associated host networks

HCMV
HAdV-A
HCV-2
HHV-6A
HSV-1

PICALM
CLU
BIN1

NFASC
NFASC

APBB2
APBB2

BACE1
BACE1

LZTR1
LZTR1

ENPP2
ENPP2

UCP54
UCP54

NCAM1
NCAM1

HADHA
HADHA

HSPA2
HSPA2

TMTC2
TMTC2

TMTC2
TMTC2

ELMO1
ELMO1

COPA
COPA

SANP056
SANP056

TRAK2
TRAK2

TRAK2
TRAK2

ZNF682
ZNF682

ZNF682
ZNF682

ITSN2
ITSN2

ITSN2
ITSN2

SF3B3
SF3B3

SF3B3
SF3B3

FMNL2
FMNL2

FMNL2
FMNL2

CARD10
CARD10

CARD10
CARD10

CNP
CNP

CNP
CNP

PRK1
PRK1

PRK1
PRK1

PDK1
PDK1

PDK1
PDK1

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Alzheimer’s Disease-Associated β-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection

William A. Eimer,1,2 Deepak Kumar Vijaya Kumar,1,2 Nanda Kumar Navalpur Shanmugam,1,2 Alex S. Rodriguez,1,2 Teryn Mitchell,1,2 Kevin J. Washicosky,1,2 Bence György,2 Xandra O. Breakefield,2 Rudolph E. Tanzi,1,2,* and Robert D. Moir1,2,3,*

1Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Charlestown, MA 02129, USA
2Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA
3Lead Contact
*Correspondence: tanzi@helix.mgh.harvard.edu (R.E.T.), moir@helix.mgh.harvard.edu (R.D.M.)
https://doi.org/10.1016/j.neuron.2018.06.030
Infection with several HHV seed rapid AB fibrillation, and that this is mediated by the beta glycoprotein, high conserved among viral species.
Amyloid overproduction had protective effect against viral encephalitis, with increased survival time, and reduced wt loss following viral injection.

**Figure 1. Aβ42 Expression Increases Host Survival in an HSV1 Encephalitis 5XFAD Mouse Model**

Female transgenic mice (5XFAD), 5–6 weeks old, expressing human Aβ were compared against wild-type (WT) littermates for survival following bilateral intracranial injections of HSV1. Following injection of viable HSV1, WT and 5XFAD mice were followed for (A) survival and (B) weight loss. No mortality was observed among sham-infected control. Statistical significance was calculated by log-rank (Mantel-Cox) test for survival and statistical means compared by t test for weight loss. Survival analysis data were pooled from five independent experiments.
Viral regulation of AD associated host networks
Impact of viral activity on genetic, transcriptomic, clinical and neuropathology networks in AD

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
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Summary

- Evidence for increased *herpesviridae* sequences in AD
  - 3 independent AD cohorts
  - 4 brain regions
  - 5 study centers
- Viral activity associates with AD biology across diverse domains
- Parsimonious with findings of virally mediated β-amyloid deposition
- Driver vs. accelerant vs. hitchhiker of disease?
Acknowledgements

NIH - Accelerating Medicines Partnership - Alzheimer’s Disease

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  Winnie Laing

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  Cory Funk

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  Nilufer Ertekin-Taner

University of Florida
  Todd Golde

Rush University Medical Center
  David Bennett

Columbia Medical Center
  Philip De Jager

ben.readhead@asu.edu
ben.readhead@mssm.edu
Estimating viral abundance in RNA and DNA sequencing data

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
eQTL of virus-host networks are enriched for AD GWAS risk loci

Readhead et al., Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, Neuron (2018), https://doi.org/10.1016/j.neuron.2018.05.023
Virally mediated neuronal loss in AD
Neuronal fraction negatively associated with AD traits

<table>
<thead>
<tr>
<th>Anterior Prefrontal Cortex</th>
<th>Superior Temporal Gyrus</th>
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Correlation

- Astrocytes
- Endothelial
- Microglia
- Neurons
- Oligodendrocytes

Clinical Density
Amyloid Plaque Score
Break & Braak Score
Clinical Dementia Rating
Amyloid Plaque
Break & Braak
Clinical Dementia Rating
Amyloid Plaque
Break & Braak
Clinical Dementia Rating
Amyloid Plaque
Break & Braak
Clinical Dementia Rating
Amyloid Plaque
Break & Braak
Neuronal fraction negatively associated with AD traits

<table>
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<tr>
<th>Neuronal Fraction</th>
<th>Anterior Prefronal Cortex</th>
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Clinical Dementia Rating, Amyloid Plaque, Braak & Braak Rating, Density, Score.
Neuronal fraction negatively associated with AD traits
Neuronal fraction negatively associated with AD traits

**d**

Viral differential RNA abundance

Viral association with neuronal fraction

**e**

Causal Inference Testing (CIT)

[vQTL]

HHV-6A or Host gene abundance

[?]

Neuronal Fraction

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<td>3.9e-03, 6.7e-03</td>
<td>HAdV-A (full)</td>
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<td>8.5e-03, 6.6e-03</td>
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<td>HHV-6A (Unique)</td>
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<td>HHV-6A (U3/U4)</td>
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<td>6.2e-03, 1.7e-03</td>
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<td>HHV-6A (full)</td>
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<td>KSHV (full)</td>
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<td>HCV-2 (full)</td>
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<td>HAdV-B2 (full)</td>
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[Gene Types]

- Astrocytes
- Endothelia
- Microglia
- Neurons
- Oligodendrocytes
Neuronal Loss Network (NLN)

Host genes regulated by HHV-6A in STG

mRNA regulators of neuronal fraction

Correlation with neighbor
Positive
Negative

NLN cis-eQTL AD risk loci enrichment
FDR < 7^-3
miR-155 network implicated in multiple regions in preclinical and clinical AD

pre AD

Gained in pre AD

NDAD_EC_DOWN
NDAD_EC_UP
NDAD_HIP_DOWN
NDAD_HIP_UP
NDAD_MTG_DOWN
NDAD_MTG_UP
NDAD_PC_DOWN
NDAD_PC_UP
NDAD_SFG_DOWN
NDAD_SFG_UP
NDAD_VCX_DOWN
NDAD_VCX_UP

Preclinical & clinical AD expression + microRNA / mRNA Networks

Liang, 2007
Liang, 2008
Liang, 2010
Hsu, 2011
Chu, 2016

miR / AD Enrichments
FDR < 0.1

Multiregional preclinical AD transcriptome
Multiregional AD transcriptome
Preclinical AD Network Drivers

hsa-miR-155-5p
hsa-let-7b-5p
hsa-miR-16-5p
hsa-miR-21-5p
hsa-miR-615-3p

microRNA / mRNA Networks

miR-155 network implicated in multiple regions in preclinical and clinical AD
miR-155 is suppressed by HHV-6A, a regulator of preclinical and clinical AD networks and alters β-amyloid plaque and oligomer formation.

APP/PS1 x MIR155-KO vs. APP/PS1
Frontal Cortex

# β-amyloid plaques

** P-value: 4−4

** P-value: 3−4

![Image of APP/PS1 and APP/PS1 x MIR155-KO with bar graph showing the number of β-amyloid plaques]
miR-155 is suppressed by HHV-6A, a regulator of preclinical and clinical AD networks and alters β-amyloid plaque and oligomer formation