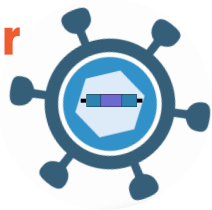
THE UNIVERSITY OF SYDNEY
Brain and Mind Centre

FORE FRONT
Cutting edge research into neurodegenerative disorders

Human Endogenous Retrovirus K (HERV-K): A novel biomarker for Alzheimer's disease and Parkinson's disease?



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ABSTRACT

Pre-symptomatic detection is vital for effective treatment in Alzheimer's disease (AD) and Parkinson's disease (PD). Novel biomarker avenues are being considered, including retrotransposons like HERV-K. Increases in HERV-K expression have been identified as a potential biomarker for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). However, little is known about changes in HERV-K expression in AD and PD. Using ddPCR, we show that HERV-K viral expression and genomic copies are decreased in PD and this is attributed to changes in HERV-K viral load, suggesting that HERV-K could serve as a potential biomarker for PD. Furthermore, we show that HERV-K viral expression and genomic copies are not altered in AD serum, and HERV-K expression does not change as AD progresses. Together, these results suggest that HERV-K is not altered in AD and thus is unlikely to be suitable as a biomarker for AD.

INTRODUCTION

AD and **PD** are the **most common** neurodegenerative diseases worldwide and pre-symptomatic detection is vital for effective treatment. Novel biomarker avenues are being considered, including **retrotransposons** such as **human endogenous retrovirus K** (HERV-K), which are genetic elements that move from one genomic location to another[1] (Fig.1).

Abnormal expression of HERV-K has been identified as a potential biomarker for ALS and FTD[2,3]. However, little is known about **changes in HERV-K expression in AD and PD**. We investigate if HERV-K expression is altered in AD and PD serum to assess the suitability of HERV-K as a biomarker for these diseases.

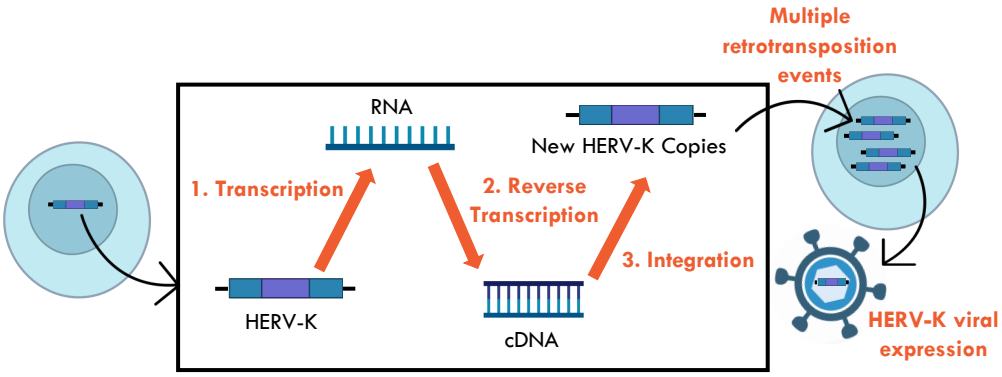


Figure 1. *Genomic HERV-K undergoes retrotransposition via a copy-and-paste mechanism, leading to multiple copies within the genome. HERV-K can then be expressed forming extracellular viral particles.*

HYPOTHESIS: HERV-K expression is altered in AD and PD serum due to changes in viral load

AIMS:

1. To determine the number of genomic copies of HERV-K in AD and PD serum
2. To determine the expression of HERV-K viral load in AD and PD serum

METHODS

Droplet Digital PCR (ddPCR) using probe-based assays

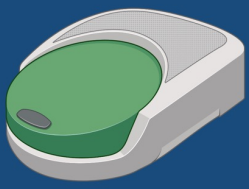
1. Human serum from AD, PD and controls

1. Whole blood from AD, PD and controls

2. Extract total nucleic acid

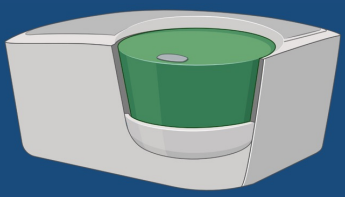
2. Extract genomic DNA

3. Generation of droplets

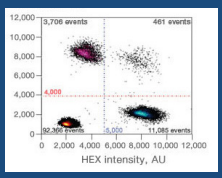


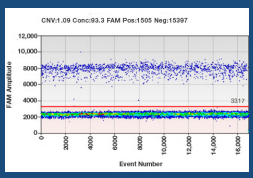
4. PCR amplification

5. Droplet reading



6. Data analysis





RESULTS

Alzheimer's Disease (AD)

Total nucleic acid
Con (n=33), AD (n=80)

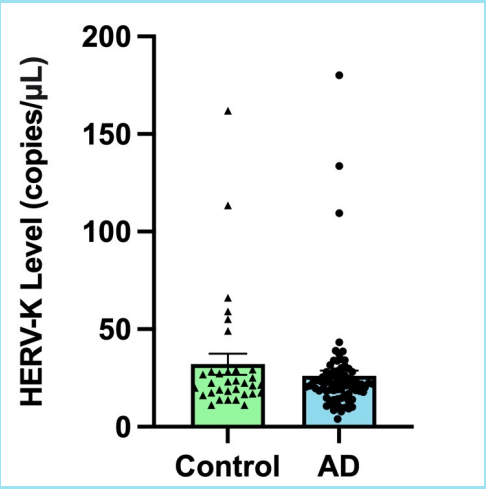


Figure 2. *HERV-K level in serum showed no significant difference between AD and controls.*

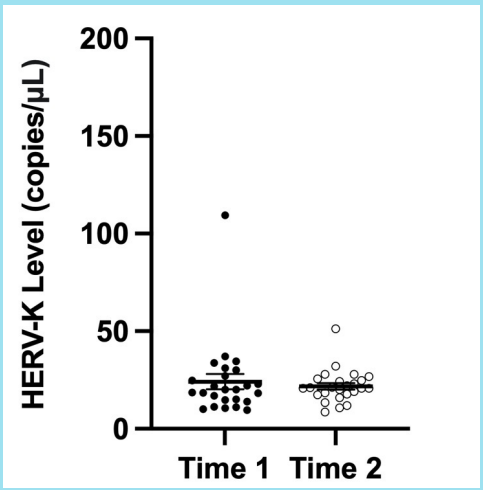


Figure 3. *Longitudinal analysis of AD serum showed no significant difference in HERV-K level between timepoints 1 and 2.*

Genomic DNA
Con (n=16), AD (n=62)

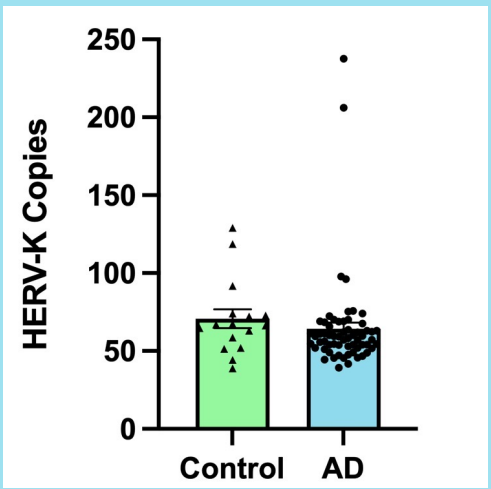


Figure 4. *HERV-K copies showed no significant difference between AD and control in genomic DNA.*

OVERALL:

→ **HERV-K is not altered in AD serum**

→ **HERV-K levels do not change during AD progression**

RESULTS

Parkinson's Disease (PD)

Total nucleic acid
Con (n=25), PD (n=27)

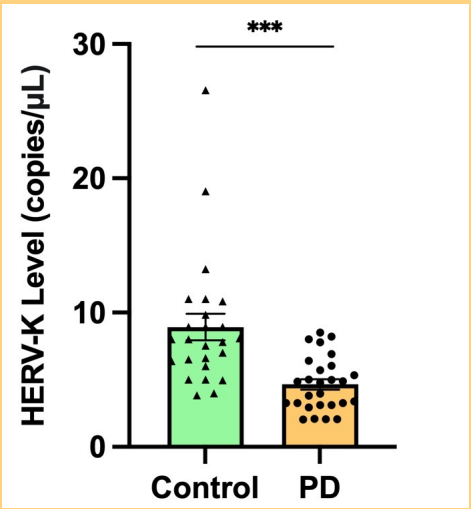


Figure 5. *HERV-K levels were significantly decreased in PD compared to control ($p<0.001$). Unpublished data (Phan, 2022).*

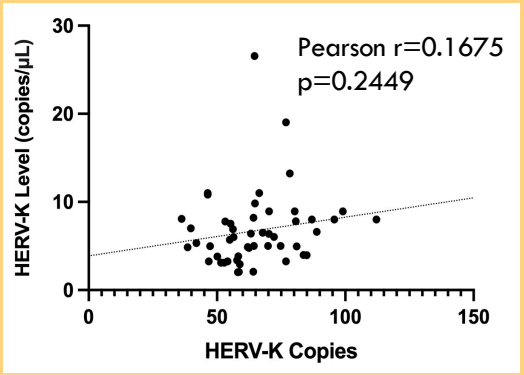


Figure 7. *Correlation of HERV-K genomic copies to HERV-K levels showed no significance.*

Genomic DNA
Con (n=25), PD (n=25)

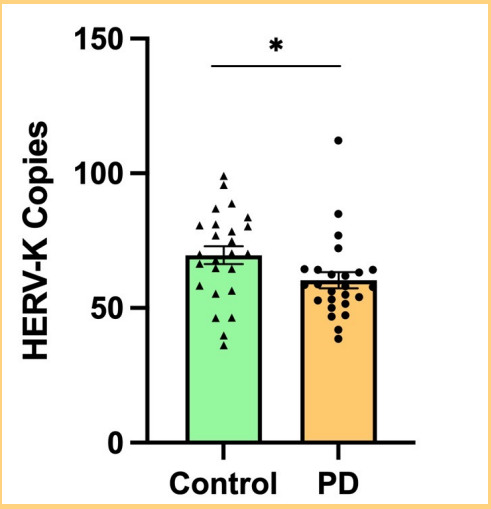
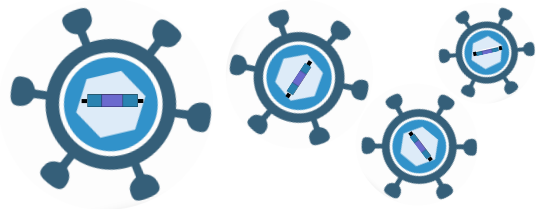


Figure 6. *HERV-K copies in genomic DNA were significantly decreased in PD compared to control ($p<0.05$)*

OVERALL:

- → **HERV-K levels are decreased in PD**
- → **HERV-K genomic copies are decreased in PD**
- → **No correlation between HERV-K levels and copies, thus decreases in serum HERV-K levels are solely due to changes in viral load**

CONCLUSION



- **Since decreases in serum HERV-K in PD are solely due to changes in viral load, HERV-K could serve as a potential biomarker for PD**
- **However, as HERV-K is not altered in AD serum, it is unlikely to be suitable as a biomarker for AD**

Future work will:

- Further investigate and confirm whether HERV-K is a suitable biomarker for PD (e.g. increase sample size, longitudinal study, investigate pathological links)
- Investigate other retrotransposons that are implicated in neurodegenerative diseases to assess their suitability as biomarkers for AD and PD

REFERENCES

1. Ochoa Thomas et al. (2020) *Current Opinion in Neurobiology*, *61*.
2. Li et al. (2015) *Science Translational Medicine*, *7*, 307.
3. Phan et al. (2021) *Communications Medicine*, *1*, 1.

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