THE IMPLICATION OF HUMAN ENDOGENOUS RETROVIRUS K IN FRONTOTEMPORAL DEMENTIA NEUROPATHOLOGY

Kelvin Le*[1,2], Katherine Phan[1,2], Glenda M Halliday[1,2], Woojin S Kim[1,2]

1The University of Sydney, Brain and Mind Centre, Sydney, Australia 2The University of Sydney, School of Medical Sciences, Sydney, Australia

ABSTRACT

Frontotemporal dementia (FTD) and motor neuron disease (MND) are neurodegenerative diseases having in common TAR DNA-binding protein 43 (TDP-43) neuropathology. Retrotransposons are mobile genetic elements with potential regulatory roles and aberrant activity of the retrotransposon human endogenous retrovirus K (HERV-K) is associated with pathological TDP-43 expression in MND. However, little is known about the role of HERV-K in FTD. This project aims to elucidate the neuropathological role of HERV-K in FTD brain. We showed increases in HERV-K *env* and TARDBP (gene encoding TDP-43) expression in FTLD and FTLD-MND brain. Furthermore, there was a strong positive correlation between *TARDBP* and HERV-K *env* expression. Findings suggest that HERV-K is implicated in FTD neuropathology.

BACKGROUND

Frontotemporal dementia (FTD) and **motor neuron disease (MND)** are neurodegenerative **TAR DNA-binding protein 43 (TDP-43) proteinopathies** existing on a disease spectrum[1] (Fig 1).

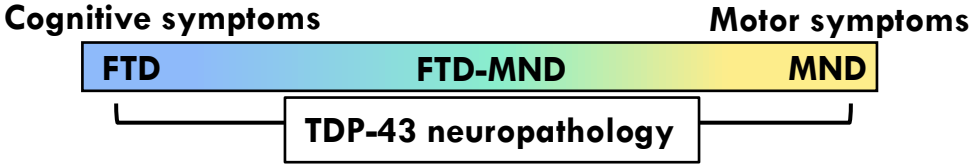


Fig 1: FTD-MND spectrum

Retrotransposons are mobile genetic elements with potential gene regulatory roles; however, aberrant retrotransposon activity is associated with neurodegeneration[1]. Particularly, the retrotransposon **human endogenous retrovirus K (HERV-K)** is associated with TDP-43 proteinopathy, specifically MND[1,2] (Fig 2).

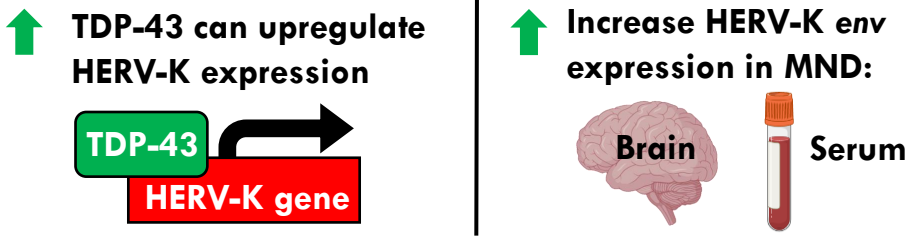


Fig 2: Association between TDP-43 pathology and HERV-K

Currently, limited studies have explored the role of HERV-K in FTD despite sharing TDP-43 neuropathology.

HYPOTHESIS: HERV-K expression is altered in FTD brain and is associated with TDP-43

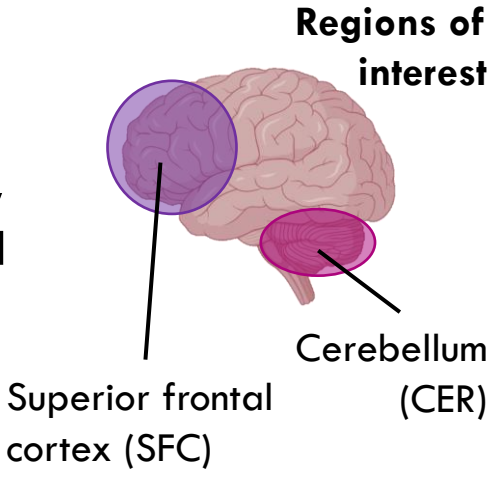
AIMS

1. Determine if HERV-K *env* expression is increased in disease-affected regions in FTD brain
2. Determine if HERV-K *env* expression is positively correlated with *TARDBP* expression (gene encoding TDP-43)

THE APPROACH

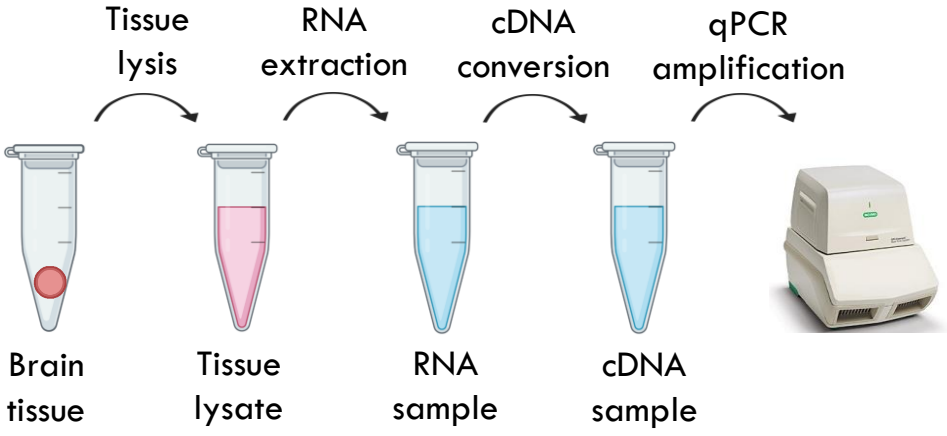
EXPERIMENTAL DESIGN

Tissue samples from patients with **FTD (n=5), MND (n=12), FTD-MND (n=6)** and **without neuropathology (CON; n=10).**



METHOD

Quantitative polymerase chain reaction (qPCR)* using SYBR green will be conducted to quantify the **relative expression of HERV-K *env* and *TARDBP***



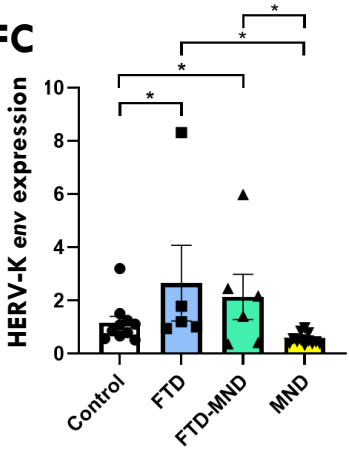
*qPCR using specific primers for HERV-K *env*, *TARDBP* and 3 housekeepers: *GAPDH*, *β-actin*, *PPIA*. Relative expression calculated using ΔΔCt method.

RESULTS

SUPERIOR FRONTAL CORTEX

Fig 3a: HERV-K *env* expression in SFC

Significant increases in HERV-K *env* expression in FTD and FTD-MND compared to MND and control (*p<0.05, adjusted for sex and post-mortem interval)



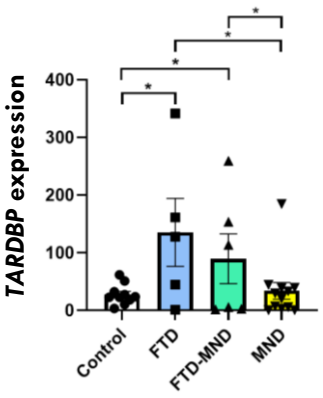
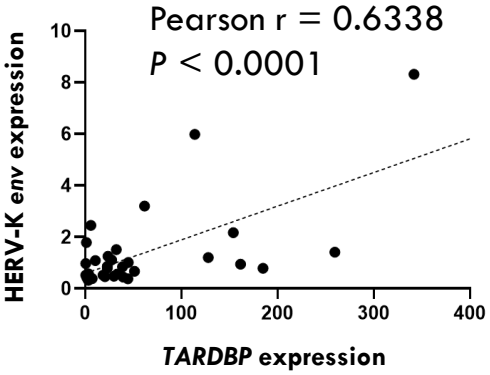


Fig 3b: *TARDBP* expression in SFC

Significant increases in *TARDBP* expression in FTD and FTD-MND compared to MND and control (*p<0.05, adjusted for sex and post-mortem interval)

Fig 3c: Correlation of *TARDBP* and HERV-K *env* in SFC; a disease-affected region

Strong positive correlation between HERV-K *env* and *TARDBP* expression in a disease-affected region.



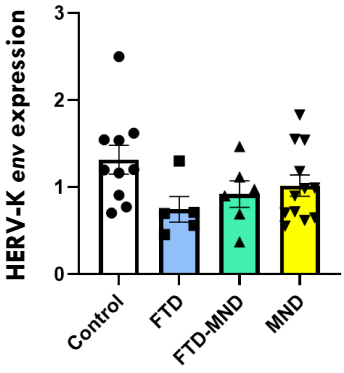
SUMMARY: HERV-K *env* expression was increased in the disease-affected region of FTLD and FTLD-MND brain compared to control and MND. HERV-K *env* expression correlated with *TARDBP* expression

RESULTS

CEREBELLUM

Fig 4a: HERV-K *env* expression in CER

No significant differences in HERV-K env expression in FTD, FTD-MND, MND cohorts compared to control.



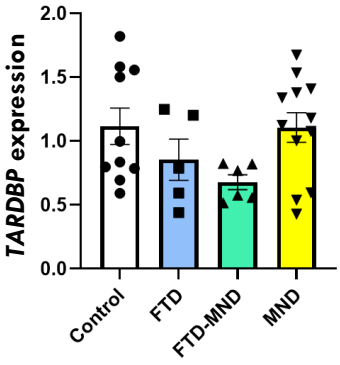
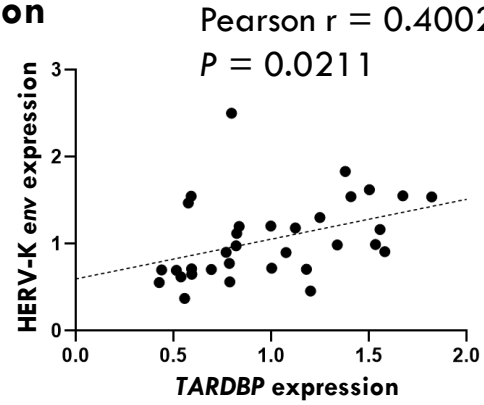


Fig 4b: *TARDBP* expression in CER

No significant differences in *TARDBP* expression in FTD, FTD-MND, MND cohorts compared to control.

Fig 4c: Correlation of *TARDBP* and HERV-K *env* in *CER*; a disease-unaffected region

Strong positive correlation between HERV-K *env* and *TARDBP* expression in a disease-unaffected region.



SUMMARY: HERV-K *env* expression was unchanged amongst all disease cohorts compared to control in the disease-unaffected region; however, HERV-K *env* expression correlated with *TARDBP* expression

CONCLUSIONS

1. HERV-K *env* and *TARDBP* (gene encoding TDP-43; a known biomarker for FTD) expression were elevated in the disease-affected region of FTLD and FTLD-MND brain.
2. Strong association between HERV-K *env* and *TARDBP* expression.
3. **HERV-K may play a role in FTD neuropathology**

FUTURE DIRECTION

Investigating HERV-K *env* protein expression in FTD brain and its association with TDP-43 levels

SIGNIFICANCE

Highlights HERV-K as a potential:

1. Biomarker for FTD and MND diagnosis
2. Therapeutic target for FTD and MND treatment

REFERENCES

1. Li, W, Lee, M-H, Henderson, L, Tyagi, R, Bachani, M, Steiner, J, Campanac, E, Hoffman, DA, Von Geldern, G & Johnson, K 2015, 'Human endogenous retrovirus-K contributes to motor neuron disease', *Science translational medicine*, vol. 7, no. 307, pp. 307ra153-307ra153.
2. Arru, G, Mameli, G, Deiana, G, Rassu, A, Piredda, R, Sechi, E, Caggiu, E, Bo, M, Nako, E & Urso, D 2018, 'Humoral immunity response to human endogenous retroviruses K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases', European Journal of Neurology, vol. 25, no. 8, pp. 1076-e84.

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