

**Title:** Expressions of specific human endogenous retroviruses of the HERV-K (HML-2) family are associated with activation and suppression of HLA class I genes in the brain

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**Abstract**

Human endogenous retroviruses (HERVs) are remnants of ancient retroviral infections integrated into the human genome throughout the ages. An estimated 8% of the genome consists of HERV proviruses, some of which can still be transcribed and even expressed as proteins. HERVs have been shown to be associated with neuroinflammation and neurodegeneration in conditions such as multiple sclerosis. Human leukocyte antigen (HLA) genes also play a role in these conditions through regulation of the immune response. As certain viruses are known to affect HLA gene expression, it is possible that HERVs could have similar effects.

The aim of the work was to investigate associations between the expression of HLA class I genes and the transcriptional activity of the proviruses of the HERV-K (HML-2) family. We utilized RNA sequencing data from 361 brain samples, focusing on 91 well preserved proviruses. Spearman's rank correlation test was used to study association between individual proviruses and HLA class I genes. GSEA (Gene Set Enrichment Analysis) was utilized to identify potential biological effects of such associations.

Significant positive correlation was found between 13 proviruses and some HLA genes, while 25 proviruses correlated negatively. GSEA indicated activation of immune functions for positively correlating proviruses and suppression of immune functions for negatively correlating proviruses.

These results suggest a functional heterogeneity of HERV-K proviruses that is locus-specific. Some may act in an immune-supportive role, reinforcing interferon/HLA pathways. Others might have been co-opted for immune dampening, possibly to avoid autoimmunity or as a viral legacy mechanism to evade immune recognition.