HERV RNA in the Brains of Patients with Multiple Sclerosis

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Introduction: Our group has used deep sequencing to identify viral RNA signatures in human brain specimens. We have previously used this method to detect HSV1, GBV-C, and measles virus sequence in brain tissue from deceased donors. Deep sequencing was performed on brain specimens from a cohort of patients who died with progressive forms of MS, revealing evidence of increased expression of some human endogenous retrovirus (HERV) domains.

Methods: Deep sequencing was performed on RNA extracted from 12 primary progressive MS, 2 neuromyelitis optica, 14 normal control, and 7 other neurologic disease (encephalitis) control frozen brain specimens. The resulting single-ended 50 bp sequences (reads) were compared to a nonredundant viral database representing all 1.2 M viral records in GenBank. A retroviral gene catalog (RVGC) was prepared by identifying human genetic loci (GRCh37.p13) homologous to domains contained in the Gypsy 2.0 retroelement database. Reads were aligned to these databases with Bowtie2. The resulting hit rates (HR) were normalized by the number of high quality reads.

Results: Fifty to 131 million high quality reads per specimen were obtained. Sequence comparisons revealed numerous significant HR differences for several HERV domains. After corrections for multiple testing within each retroviral domain, 2 GAGs and one KRBA sequence record were significantly enriched among the MS samples compared to the normal controls. Average HRs were calculated for each domain type – AP (protease), GAG, ENV, INT, RT, and KRAB. A dendrogram constructed from hierarchical clustering was used to discriminate MS and control specimens. Based on overexpression in the MS samples, 16 different MS candidate GAG and ENV domains have been selected for follow up RT-qPCR.

Conclusions: These data demonstrate that some HERV and KRAB domains are significantly overrepresented in these MS brain tissue specimens. This supports the hypothesis that expression of endogenous retroviral sequences is contributing to MS pathogenesis, potentially reconciling the autoimmune and infectious nature of this challenging disease.


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