A Pathologic Triangle: Herpesviruses, Autophagy Genes, and Alzheimer's Disease

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Since the 1960s, experts have speculated that herpesviruses may be a contributing cause of Alzheimer's disease (AD). Previously, the molecular connections between the amyloid precursor protein (APP) and type 1 herpes simplex virus (HSV-1) have been described. Additionally, others have reported molecular connections between HSV-1 and autophagy using samples from four different brain regions taken from post-mortems of people who had and had not had cognitive impairment before they passed away. In 2018, Readhead et al. discovered molecular-genetic evidence that HSV-1, HSV-2, HHN6, HHN7, VZV, and CMV activity is associated with AD. The most notable of these was the common virus known as HHN6, which causes a slight pediatric disease. A network of potential AD-associated genes was found using a quantitative trait loci (QTL) technique that corresponded with viral activity and load. These ontology networks did not take autophagy genes (ATG) into account specifically. Our hypothesis is that viral infections interfere with cellular membrane functions, changing autophagic activity. People who have genetic variants that guard against this dynamic would either have lower virus loads or would be less susceptible to cognitive impairment. In the beginning, we created a comprehensive list of ATG, including 180 that we specifically found through machine learning, using data collected from literature and websites. We used software created by Readhead et al. 2018 and made available through Synapse.com to sequence post-mortem brain data taken from publications and open websites provided by brain banks run by the Alzheimer's Center. Next, we used data mining techniques to search the list of QTL that were associated with elevated viral load and activity for ATG across 300+ brains from the Nun's Study and Mount Sinai Brain Banks. Finally, we compared the expression levels of these ATG in control and preclinical AD with those ATG-associated QTL. From published data, we determined the ATG expression levels that were associated with pre-clinical AD or non-AD and no dementia. When compared to non-AD controls in pre-clinical studies, almost all ATG were downregulated. We discovered a correlation between single nucleotide polymorphisms linked to higher viral load and lower expression of certain ATG in AD. In this study, 8 ATG from the comprehensive list have been proposed to support the idea that autophagy is a unique mechanism linking herpesvirus to AD, which may help identify new targets for diagnostic and therapeutic interventions. Finding genetic susceptibilities to the survival and advancement of the herpesvirus may be crucial for the future prevention of adult AD because HHV6 infects a huge population throughout childhood.

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