Herpesviruses may contribute to Alzheimer's disease via transposable elements

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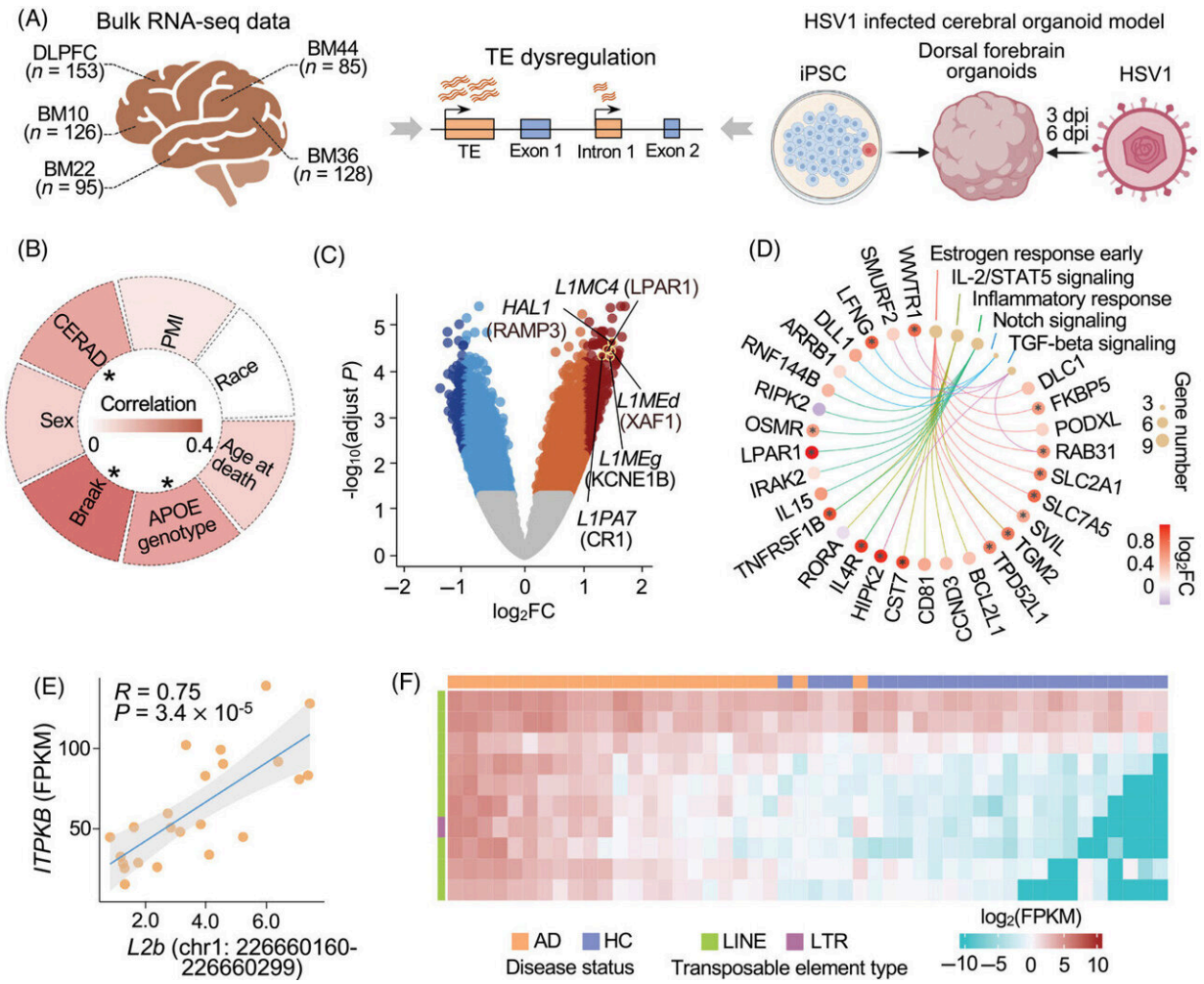

TE dysregulation in HHV-positive AD brains. Credit: *Alzheimer's & Dementia* (2025). DOI: 10.1002/alz.14595

Researchers from Cleveland Clinic's Genome Center have outlined the pathway human herpes simplex virus-1 (HSV1) can use to contribute to Alzheimer's disease in aging brains. In a report published in *Alzheimer's & Dementia*, investigators also share two FDA-approved, commercially available drugs that reverse this pathway in a laboratory setting.

The findings are the first concrete evidence to support the previously controversial link between human herpesviruses (HHVs) and Alzheimer's disease. Illustrating the potential for herpes to trigger dementia aids continued efforts to prevent and cure neurodegenerative disease, says senior author and Genome Center director Feixiong Cheng, Ph.D..

For most people, contracting a herpes infection is just an inconvenient or harmless fact of life. Many herpesviruses are individually present in a large percentage of people worldwide, meaning virtually every human being on earth is expected to contract at least three types of herpesviruses by adulthood. Some of these viruses don't cause symptoms, while others only cause minor illnesses like mono or chickenpox. However, even after these illnesses subside, an infected individual still carries herpesviruses for the rest of their life, with only minor symptoms like occasional cold sores.

While herpesviruses are generally harmless when they are suppressed, mounting evidence shows that our immune systems can lose the ability to suppress them. This can happen naturally as we age, during pregnancy and after an illness. Recent research has shown that as herpesviruses become more active, they can trigger diseases including pregnancy complications, birth defects or developmental delays in our children and even cancer.

It is becoming clear that HSV and other herpesviruses are risk factors for diseases of old age that are underexamined, Dr. Cheng says.

Circumstantial evidence has linked HSV-1 to Alzheimer's disease, but there was no explanation for how these phenomena were linked.

Dr. Cheng hypothesized that latent HSV-1 infections could trigger Alzheimer's disease by directly activating the transposable elements the Cheng Lab had previously connected to disease progression in aging brains. Transposable elements are small pieces of DNA that can activate to physically "jump" out of our chromosomes and randomly move to far-away regions of our DNA. The elements re-integrate into these new regions of our genome, disrupting the function of the genes they interrupt. Almost half of our DNA is made up of transposable elements, and the elements become more active as we age.

After mapping all transposable elements that are associated with Alzheimer's disease in aging brains, investigators analyzed four publicly available datasets which contained RNA sequencing data from hundreds of healthy and Alzheimer's-affected brain cells. The Cheng Lab received collaboration and help interpreting their data from Jae Jung, Ph.D., chair of Infection Biology; James Leverenz, MD, formerly of Cleveland Clinic's Lou Ruvo Center for Brain Health; and collaborators from Case Western Reserve University and the University of Nevada Las Vegas.

The team identified several TEs that were more highly activated in Alzheimer's-affected brains that contained HSV RNA, compared to uninfected or healthy brains. They then tested HSV-1 infected brain cells to see whether the identified TEs were activated, as well as the effects on neuroinflammation and accumulation of proteins associated with Alzheimer's disease.

The result was a step-by-step guide on the connection between HSV-1 and the hallmarks of Alzheimer's disease:

1. An individual contracts HSV-1, or their latent HSV-1 infection

becomes more active as a natural consequence of age;
2. The HSV-1 is linked with transposable element (like LINE-1) activation;
3. The transposable elements disrupt key genetic processes in the brain that are associated with an accumulation of tau and similar Alzheimer's-associated proteins;
4. The accumulated proteins contribute to inflammation and neurodegeneration.

The investigators then used artificial intelligence to analyze 80 million publicly available patient health records to see if individuals who were prescribed antiviral herpes medications went on to receive fewer Alzheimer's diagnoses later in life. The herpes medications valacyclovir and acyclovir were associated with significantly reduced instances of Alzheimer's disease. Treating laboratory models with these drugs seemed to reverse the infection to the Alzheimer's disease pathway, mechanistically supporting what they observed in real-world patient data.

"These results further suggest potential relationships between HSV-1 infection and Alzheimer's disease and provide two potential drug candidates that may provide treatment for a disease that currently has no cure," Dr. Cheng says. "We hope our findings, if broadly applied, can also provide new strategies for treating other neurological diseases associated with herpesviruses or other viruses."

More information: Yayan Feng et al, Human herpesvirus-associated transposable element activation in human aging brains with Alzheimer's disease, *Alzheimer's & Dementia* (2025). DOI: 10.1002/alz.14595

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