

# Cold sore virus might play role in Alzheimer's

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A gene known to be a major risk factor for Alzheimer's disease puts out the welcome mat for the virus that causes cold sores, allowing the virus to be more active in the brain compared to other forms of the gene. The new findings, published online in the journal *Neurobiology of Aging*, add some scientific heft to the idea, long suspected by some scientists, that herpes somehow plays a role in bringing about Alzheimer's disease.

The work links a form of the ApoE gene known as ApoE-4, which after advanced age is the leading known risk factor for getting Alzheimer's disease, with the form of herpes – herpes simplex 1 or HSV – that infects more than 80 percent of Americans and causes cold sores around the mouth. The findings from a group at the University of Rochester Medical Center show that the particular form of the gene that puts people at risk also creates a fertile environment for herpes in the brain, allowing the virus to be more active than other forms of the ApoE gene permit.

Scientists have known for more than 15 years that the ApoE-4 gene is a player in Alzheimer's disease, but the idea that it works in concert with the herpes virus is new.

"This work raises the question whether herpes in concert with ApoE-4 increases the risk of Alzheimer's disease. The data suggests that ApoE-4 may support the ability of HSV to be a more virulent pathogen," said Howard Federoff, M.D., Ph.D., the leader of the team and professor of Neurology, Medicine, and Microbiology & Immunology. He worked

closely with post-doctoral research associate Renee Miller, Ph.D., on the project.

The findings, which are based on measurements of the activity levels of the herpes virus in the brains of mice with different forms of the human ApoE gene, bring together several lines of research that have pointed toward a possible role for herpes in Alzheimer's disease.

Ruth Itzhaki of the University of Manchester has led the way with several studies showing a correlation between herpes and Alzheimer's. She has shown that Alzheimer's patients who have the ApoE-4 form of the gene have more herpes DNA in the brain regions that are affected by Alzheimer's, compared to Alzheimer's patients who also have herpes but who have a different form of the ApoE gene. And she has shown that people with the ApoE-4 version of the gene who are infected with herpes are more likely to get Alzheimer's disease than people infected with herpes who have a different form of the ApoE gene, or than people who have the ApoE-4 gene but who don't have herpes.

Other scientists have found that a herpes infection is active more often – causing the tell-tale cold sores around the mouth – in the 25 percent of people who have a copy of the ApoE-4 gene. In other words, people who are frequently troubled by cold sores are more likely to have the gene that makes them more vulnerable to Alzheimer's disease.

Cold sores that come and go are the outward sign of the two different phases of the virus's life cycle. Herpes simplex is a chronic infection that lives in a person for a lifetime, periodically flaring up in a "lytic" phase where it causes cell damage, then retreating and seeking safe harbor within the body's nerves in a "latent" phase. The virus spends most of its time in the latent phase, sequestered in cells, not active and not replicating. But occasionally, when triggered by factors like stress, fatigue, certain foods, or even sunlight, the virus becomes active,

traveling from its hiding places in the nervous system to cells around the mouth, damaging cells and causing cold sores.

It was this cycle of activity and latency that Miller and Federoff focused on while looking at the brain cells of mice with different forms of the ApoE gene. They looked at four groups of mice: Some had ApoE-3, which is what the majority of people carry; some had ApoE-4, which in people makes them more likely to get Alzheimer's; some had ApoE-2, which makes people less likely to get the disease; and some had no ApoE gene at all.

The team found that the virus infiltrates brain cells about the same no matter which gene is involved. But they found that the subsequent activity level of the virus generally mirrored the disease-causing potential of the gene. They found that in animals with the ApoE-4 gene, the virus is less likely to be in the quiet, latent stage of its life cycle, suggesting it has more of an opportunity to replicate. In animals with the ApoE-2 gene, the virus was less active.

The work suggests that ApoE-4 may alter the balance between the HSV life cycle forms. It's possible that the ApoE gene works as a sort of bodyguard that tries to keep cells safe from herpes, perhaps by facilitating latency. Somehow the ApoE-2 version is extremely effective at keeping the virus at bay, while in this study, the ApoE-4 version wasn't any more effective than not having an ApoE gene at all.

The ApoE gene is well known to Alzheimer's researchers. The gene, which normally plays a role in ferrying cholesterol around the body, is associated with both the cellular tangles and amyloid plaques that are found in the brains of patients with the disease. Researchers have found several ways in which the gene might make a person vulnerable to getting a disease like Alzheimer's. In people with the ApoE-4 gene, brain cells don't seem to recover as well from injury, and the cells don't form

new connections as well as cells equipped with either ApoE-2 or ApoE-3. Other scientists have shown that the gene plays a role in clearing toxic amyloid beta from the brain.

"Just how ApoE-4 makes people vulnerable to Alzheimer's disease isn't resolved at all," said Federoff, who is director of the University's Center for Aging and Developmental Biology. "It may be that it works in multiple ways."

The team is exploring different ways that herpes might affect the development of Alzheimer's disease. In one study the team looking at the role of Nectin-1, a cell adhesion molecule that herpes uses as one route to infect a cell. Nectin-1 plays a crucial role in forming synapses, the structures between brain cells that move information and signals from one cell to the next. The team is studying whether herpes somehow disturbs the receptor, possibly altering the structure and function of the synapse. Damage to synapses is one of the earliest signs of Alzheimer's disease.

Another possibility is that the body's immune response against herpes somehow damages the brain, and that such damage is worse in people with the ApoE-4 copy of the gene. Earlier this year Federoff's team published a study that showed inflammation is the earliest change that could be detected in a brain affected by Alzheimer's disease, before any of the hallmark plaques or tangles and certainly long before any behavioral changes are seen. Such inflammation often is a byproduct when the immune system fights an infection.

Source: University of Rochester Medical Center

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