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Gene mutation alone causes transmissible prion disease

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For the first time, Whitehead Institute researchers have shown definitively that mutations associated with prion diseases are sufficient to cause a transmissible neurodegenerative disease.

The discovery is reported in the August 27 edition of the journal *Neuron*.

Until now, two theories about the role mutations play in prion diseases have been at odds. According to one theory, mutations make carriers more susceptible to prions in the environment. Alternatively, mutations themselves might cause the disease and the spontaneous generation of transmissible prions.

Prions cause several diseases, including Creutzfeldt-Jakob disease (CJD) in humans, bovine spongiform encephalitis (BSE, or "mad cow disease") in cows, and scrapie in sheep. Some prion diseases, like BSE, can be transmitted from feed animals to humans. Deciphering the origins of prion diseases could help farmers and policy-makers determine how best to control a prion disease outbreak in livestock and to prevent prion transmission to humans.

Prions are misfolded versions of a protein called PrP. In its normal form, PrP is expressed in the brain and other neural tissues. But specific events, such as exposure to prions from the environment, can cause PrP to change from its normal shape to that of a prion. Once in the prion shape, the protein can convert other normal PrP proteins to the abnormal

shape. As PrP proteins convert to prions, they form long chains that damage brain and nerve cells, causing the neurodegenerative and behavioral symptoms characteristic of prion diseases.

To determine if a mutation in the PrP gene can cause a transmissible prion disease, Walker Jackson, first author of the *Neuron* article and a postdoctoral researcher in the lab of Whitehead Member Susan Lindquist, engineered a knock-in mouse expressing a PrP gene carrying the mutation associated with the human prion disease fatal familial insomnia (FFI).

In knock-in experiments, the researcher removes a gene of interest, makes specific changes to it in a test tube, and then places it back in its original place in the genome. In this case, Jackson replaced the mouse PrP gene with an altered version carrying the FFI mutation. This version also carried a sequence from human PrP that prevented the mice from acquiring normal mouse prions that could potentially be in the environment.

"It's more difficult to create a knock-in mouse, instead of randomly integrating the mutated gene into the mouse's genome," says Jackson. "But creating a knock-in like this makes sure the gene is expressed when and where it normally would be. That's the number one reason we think this disease model worked so well, compared to others' experiments."

As adults, the mice exhibited many of the same traits as human FFI patients: reduced activity levels and sleep abnormalities. When Jackson examined the mice's brains, they resembled those of human FFI patients, with prominent damage to the thalamic region of the brain.

After establishing that the mice have the behavioral and pathological characteristics of FFI, Jackson injected diseased brain tissue from the FFI mice into healthy mice. The healthy mice also carried the same

human derived barrier as the FFI mice, preventing their infection by normal mouse prions and ensuring that the only prion they could acquire was the one engineered by Jackson. After injection with the affected tissue, the healthy mice exhibited similar symptoms and neuropathology as the mice with the FFI mutation.

The mutated gene engineered by Jackson had created a transmissible prion disease that could not be attributed to any prions in the environment.

"One of the major tenets of the prion hypothesis is that a single amino acid change in PrP, associated with human disease, is sufficient to cause the spontaneous production of infectious material," says Lindquist, who is also a professor of biology at MIT and a Howard Hughes Medical Institute investigator. "Many people have tried and come close. But this is the first time it has been nailed."

More information: "Spontaneous generation of prion infectivity in fatal familial insomnia knock-in mice"; *Neuron*, August 27, 2009

Source: Whitehead Institute for Biomedical Research (news : web)