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Mouse model of prion disease mimics diverse symptoms of human disorder

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A comprehensive mouse model of inherited prion disease exhibits cognitive, motor, and neurophysiological deficits that bear a striking resemblance to the symptoms experienced by patients with the human version of "mad cow disease," Creutzfeldt-Jakob disease (CJD). The research, published by Cell Press in the November 26th issue of the journal *Neuron*, provides exciting insight into the mechanism of disease and may lead to the development of new therapeutic strategies for this devastating neurodegenerative disorder.

Mutation in the D178N/V129 prion protein (PrP) is associated with a subtype of CJD characterized by early cognitive impairment with memory deterioration, behavioral and motor abnormalities, electroencephalographic (EEG) changes, and specific neuropathological alterations. To date, only two transgenic models of inherited prion disease exist, which develop motor deficits but do not recapitulate the cognitive and neurophysiological abnormalities typical of CJD.

"We need experimental models with a broader spectrum of clinical signs for insight into the mechanisms of neuronal dysfunction and its evolution, and to identify earlier markers of clinical disease when therapeutic intervention may be effective," says senior study author Dr. Roberto Chiesa of the "Mario Negri" Institute for Pharmacological Research in Milan, Italy. Dr. Chiesa and colleagues developed a new transgenic mouse model of CJD expressing the mouse homolog of the D178N/V129 mutation.

The mice, called Tg(CJD) mice, show motor symptoms, but also memory impairment and neurophysiological deficits, specifically EEG abnormalities and sleep alterations, strikingly similar to those observed in a CJD patient with the same mutation. The researchers also observed several neuropathological abnormalities in the Tg(CJD) mice, including alterations in the endoplasmic reticulum (ER), the neuronal protein trafficking machinery, and an associated intracellular retention of mutant PrP. This suggests that ER dysfunction might contribute to CJD pathology.

These findings demonstrate that Tg(CJD) mice faithfully mirror clinical and pathological symptoms associated with CJD. "Our results establish the first animal model of a genetic prion disease recapitulating cognitive, motor, and neurophysiological abnormalities of the human disorder," explains Dr. Chiesa. "This new model allows in-depth analysis of the disease mechanisms and may be useful for testing potential therapies for inherited prion diseases."

Source: Cell Press