Mutant prion protein could help reveal neurodegenerative disease mechanisms

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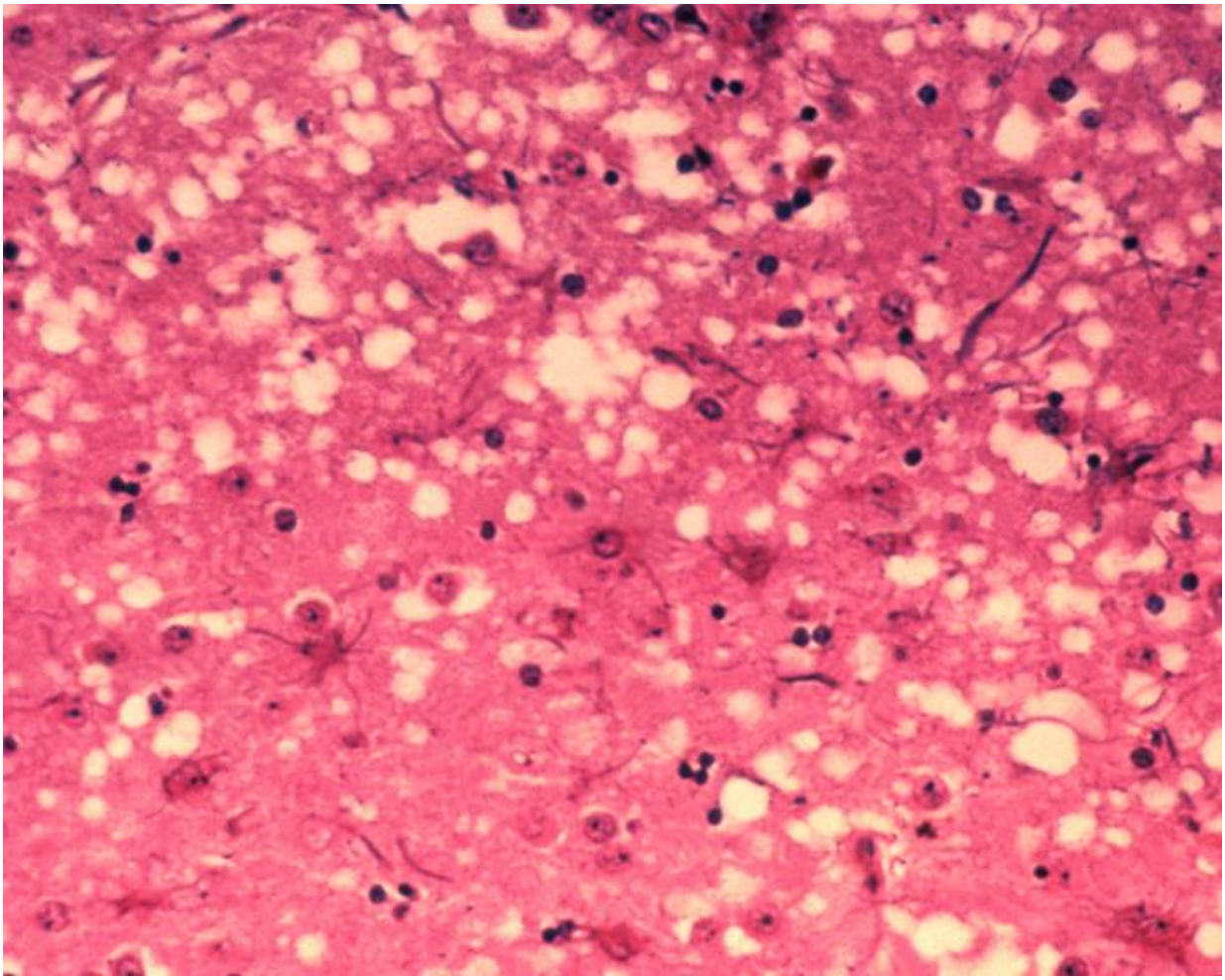

Prion fibers. Credit: AJC1 via flickr

For the first time, scientists have isolated a mutated prion protein that can multiply in the lab but not in living animals, according to a *PLOS Pathogens* study. The mutant prion provides new insights into the mechanisms that make prions infectious, says co-author Ilaria Vanni of the Department of Veterinary Public Health and Food Safety, Istituto Superiore di Sanità, Rome, and colleagues.

Prions are cellular proteins that have become mis-folded and can trigger other proteins to mis-fold, aggregate into dense protein structures, and cause brain damage. Prions are responsible for several infectious fatal neurodegenerative disorders, including Creutzfeldt-Jakob disease in humans and "mad cow disease" in cattle.

Previous research has shown that, under certain conditions, prion strains can mutate—change their conformation. In the new study, Vanni's team induced the emergence of a prion mutant while working with highly diluted natural prions obtained from sheep suffering from a prion disease called scrapie.

Like other prions, the mutant scrapie prion was able to multiply in the lab outside of an animal, in vitro. However, when the researchers infected bank voles with the mutant protein, none of the voles showed signs of disease. In contrast, the natural, un-mutated form of the prion was able to successfully infect bank voles.

The mutant prion's inability to infect voles may be due to its missing a stretch of amino acids that is present in the un-mutated form. The researchers hypothesize that this region is essential for animal infection, but not for in vitro multiplication. Future studies could build on this finding to pinpoint key prion features that affect infectivity, improving understanding of these deadly proteins.

"By investigating the in vitro evolution of prion populations derived

from natural scrapie," the authors explain, "we found that the cloud of conformational variants also includes 'defective' variants which are unable to self-sustain in vivo. The existence of natural conformational variants able to self-replicate in vitro but not in vivo will hopefully contribute to find out the molecular mechanisms allowing misfolded prion protein conformers to become deadly prions."

More information: Vanni I, Migliore S, Cosseddu GM, Di Bari a11111 MA, Pirisinu L, D'Agostino C, et al. (2016) Isolation of a Defective Prion Mutant from Natural Scrapie. *PLoS Pathog* 12(11): e1006016. DOI: 10.1371/journal.ppat.1006016