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**A Red Flag for a Neurodegenerative Disease That May Be Transmissible**

Animal experiments show how a just-discovered prion triggers a rare Parkinson’s-like disease

By [Simon Makin](http://www.scientificamerican.com/author/simon-makin) | September 1, 2015

Scientists claim to have discovered the first new human prion in almost 50 years. Prions are misfolded proteins that make copies of themselves by inducing others to misfold. By so doing, they multiply and cause disease. The resulting illness in this case is multiple system atrophy (MSA), a neurodegenerative disease similar to Parkinson's. The study, published August 31 in *Proceedings of the National Academy of Sciences*, adds weight to the idea that many neurodegenerative diseases are caused by prions.

In the 1960s researchers led by Carleton Gajdusek at the National Institutes of Health transmitted kuru, a rare neurodegenerative disease found in Papua New Guinea, and Creutzfeldt–Jakob disease (CJD), a rare human dementia, to chimpanzees by injecting samples from victims' brains directly into those of chimps. It wasn't until 1982, however, that Stanley Prusiner coined the term prion (for “proteinaceous infectious particle”) to describe the self-propagating protein responsible.

Prusiner and colleagues at the University of California, San Francisco, showed this process caused a whole class of diseases, called spongiform encephalopathies (for the spongelike appearance of affected brains), including the bovine form known as “mad cow” disease. The same protein, PrP, is also responsible for kuru, which was spread by cannibalism; variant-CJD, which over 200 people developed after eating beef infected with the bovine variety; and others. The idea that a protein could transmit disease was radical at the time but the work eventually earned Prusiner the 1997 Nobel Prize in Physiology or Medicine. He has long argued prions may underlie other neurodegenerative diseases but the idea has been slow to gain acceptance.

In 2013 a team in Prusiner's lab, including neuroscientist Kurt Giles, were trying to transmit Parkinson's disease to mice genetically engineered to produce a human protein involved in Parkinson’s, alpha-synuclein, by injecting them with brain samples from deceased patients. They failed, but for comparison they also used two MSA samples—those mice got sick. “The controls were the ones that worked,” Giles says. “So we got lots more samples.” For the new study, the team obtained 12 more MSA samples from three brain banks in London, Boston and Sydney.

The result was the same: the mice injected with these samples all developed disease within 3.5 to five months. The gene inserted in the mice has a mutation associated with a hereditary form of Parkinson's, which researchers think makes the alpha-synuclein more likely to misfold. Mice with two copies develop disease spontaneously, after about 10 months, but mice with one copy remain healthy. Injecting either type with MSA samples resulted in neurodegeneration and death for both in the same short time span.

Presumably what happens is that alpha-synuclein prions in the MSA brain samples propagate by inducing the human alpha-synuclein proteins in the mice, which are prone to misfold, to take their particular aberrant shape Afterward, these mice's brains also showed buildups of alpha-synuclein in cells, and samples from these brains also caused disease in other mice. Neither a sample from a disease-free brain nor samples from Parkinson's patients, had these effects.

PrP prions have different strains, resulting in different diseases. Researchers think this is due to alternative shapes the protein can take, which can have different properties. The same principle may apply to other types of prion. Samples from the brains of mice with two copies of the gene also caused disease when injected into other mice, but only after the longer, 10-month period. “The time it took to get disease when we used the spontaneously sick animals was very different,” Giles says. “That's clear evidence these are two different strains of prion.” The fact that Parkinson’s didn't transmit suggests that if alpha-synuclein prions are involved in Parkinson's, they are a different strain again to those causing MSA.

Affecting three in 100,000 people over 50 years of age, MSA is rarer than Parkinson's but more common than CJD. Symptoms include movement and balance impairment, along with loss of bladder control and blood pressure. Death occurs in five to 10 years and no treatments exist. It is often misdiagnosed as Parkinson’s because the two share early symptoms. Parkinson's is sometimes treated with neurosurgical procedures, which raises a concern. Although the resistance of MSA prions to standard decontamination procedures is not yet known, the measures don't eliminate PrP prions, which have on occasion been transmitted via neurosurgical equipment. The team recommends adopting the same precautions in research and neurosurgery with alpha-synuclein pathology patients as with CJD cases.

Much evidence now supports the idea that many neurodegenerative diseases share this core mechanism of self-propagating proteins that accumulate and ultimately kill cells. Similar findings have been reported for amyloid beta, the protein that accumulates in Alzheimer's disease, although typically in terms of increasing damage, rather than transmission. “I think Prusiner's concept is valid—it's just important to be a bit careful about what you call a prion,” says Lary Walker, a neuroscientist at Emory University who was not involved with the study. “All these other diseases arise spontaneously within the brain; there's no evidence they're infectious by any standard definition of the word.” Walker and colleagues argue for changing the definition to proteinaceous *nucleating* particle. But the number of cases of prion disease from transmission, in humans, is actually tiny as a proportion. “The vast majority are sporadic, then genetic, then a tiny minority from infections,” Giles says. “A big difference is there aren't equivalents of Alzheimer's, Parkinson's and MSA in animals, and we don't generally eat humans.”

The team has also developed a faster method for testing transmission, using human cell cultures containing the same mutant alpha-synuclein gene. This method also showed transmission of MSA, but in four days instead of four months. This could prove a huge boon to researchers trying to develop treatments. “Having cell assays that respond to a specific disease allows us to rapidly investigate how these diseases spread in patients,” says postdoc Amanda Woerman, also in Prusiner’s lab, who led a companion study focusing on the human cell line, published earlier this month. “Understanding this unifying mechanism provides us with an opportunity to develop interventions capable of preventing disease progression.”

Walker agrees: “It compels the community to focus on the right part of the problem,” he says. “By focusing on the simplicity of the molecular mechanism, you can make sense of a lot of seemingly disparate diseases.”