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Study finds two gene classes linked to new prion formation

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Unlocking the mechanisms that cause neurodegenerative prion diseases may require a genetic key, suggest new findings reported by University of Illinois at Chicago distinguished professor of biological sciences Susan Liebman.

Prions can turn a normal protein into a misfolded form. One prion in mammals promotes progressive neurodegenerative disorders like "mad cow" disease that often prove fatal. But how this process happens remains an open question for scientists.

Prions have been found to exist in a wide range of organisms. Those in brewer's yeast, which researchers like Liebman study, provide critical insight into how prions work.

Prion proteins in yeast aggregate, while non-prion proteins do not. Aggregation of new prions happens spontaneously -- but, in the natural world, very slowly.

Anita Manogaran, a former UIC research assistant professor in biological sciences, working with Liebman, sped-up prion formation to identify genes important in the process. The researchers were also able to monitor different stages of prion appearance by tagging prion proteins with another protein that fluoresces green. Cells in the process of forming prions had fluorescent rings, which could give rise to cells with prions.

"We learned there are some genes important for the generation of prions," Liebman said.

Some 400 yeast genes were screened for the ability to prevent the new appearance of yeast prion proteins.

"Through a number of screens, we came down to a much smaller number (of genes) that inhibited prion appearance," Liebman said. These genes fell into two classes -- one that could still make the rings, which is the hallmark of the beginning of prion aggregation. But the other class of genes had trouble forming rings, Liebman said.

Liebman and Manogaran also looked beyond new prion formation to see if these same genes had an effect on toxicity associated with a protein that causes Huntington's disease -- a fatal human neurodegenerative disorder.

"We found that genes that could make rings also were more toxic in the presence of the Huntington's disease protein," Liebman said. "If no rings were made, they were less toxic."

The full implications of the findings are not yet understood, Liebman cautioned.

"The more we understand about these mechanisms and the genes that are involved, the more we'll be able to understand the new appearance of prion disease -- like Creutzfeldt-Jakob and 'mad cow' -- and Huntington's disease. The more we understand what affects toxicity, the more we'll understand why these are toxic."

The findings were reported in the May 19 issue of *PLoS Genetics.*