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Change in Single Gene Causes Degenerative Brain Disease in Mice

Mice whose brains receive half the dose of a critical growth-regulating gene exhibit the altered behaviors and nerve cell tangles common in people with Alzheimer's disease or dementia, according to a new report by Howard Hughes Medical Institute (HHMI) scientists.

The study, led by HHMI international research scholar Freda Miller, shows that changing just one copy of the *p73* gene threw off the balance between cellular life and death in the brain.

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- Freda D. Miller

"The big shock was that half the level of just one gene had such a big impact," explains Miller, who is at the Hospital for Sick Children in Toronto. Finding a single protein with such a large impact on anatomy and behavior is an important step toward understanding and treating neurodegenerative diseases.

Miller and David Kaplan at the University of Toronto led the research team, which reports their finding in the September 11, 2008, issue of the journal *Neuron*.

As the brain develops, neural cells and connections that are no longer needed are pruned away. A number of different molecules determine when to kill off nerve cells that are damaged or no longer needed. To balance the molecules that bring about cell death, other molecules, like the p73 protein, play an "anti-death role" in the brain, Miller's team reported in a *Science* paper in 2000. "There are a number of checkpoints to keep cells from writing

themselves off,” she says.

More recent investigations found that some patients with Alzheimer's disease naturally lack one copy of the *p73* gene, and likely have lower p73 protein levels as a result. Those findings did not necessarily mean that lower levels of p73 contribute to Alzheimer's, but they strongly suggested that the protein may protect healthy individuals.

Looking for a more definitive answer, Miller's team studied genetically engineered mice that were born with only one copy of the *p73* gene. The mice lacking one copy of *p73* behaved differently than normal mice, and the differences increased as they grew older. For example, Miller's team found that mice with reduced *p73* took longer to find their way out of a water maze than normal mice. They also displayed an unusual behavior clasping their legs together when held up by their tails. “Instead of splaying their legs out, they clasped them into their bodies,” Miller says. “My postdoc came and said, ‘Freda, these mice are acting very strangely.’”

Miller's team then searched for anatomical evidence that the reduction in p73 was affecting the brains of the mice. Using magnetic resonance imaging, the researchers found that the motor cortex and several other regions of the brain had 5-16 percent less volume than the same areas in healthy mice.

Later, when they dissected the brains, they found accumulations of Alzheimer's-related tangles inside and outside cells, composed mostly of a nervous system protein called tau that incorrectly attached to phosphate molecules. “Accumulation of the aberrant form of tau and tangles is bad for your brain,” Miller says.

It is still unclear how these accumulations harm the brain, but they are common in patients with neurodegenerative diseases. P73 may indirectly regulate the formation of tangles in its role as an anti-death cell monitor.

Miller's next step is to see if reductions in p73 have the same impact in humans. The team will look for changes in the number of copies of the p73 sequence in a larger population and see whether a reduced amount of p73 is more common in people with neurodegenerative disorders than in the healthy population, Miller says.

“The good news is this isn't a situation where people are completely missing this gene,” Miller says. The people already found to have variations in *P73* genes tend to have some p73 production capacity, which might be exploited and improved with drugs. For instance, “we already know that growth factors really increase levels of the normal, pro-life version of p73.”

The mixture of molecules required to sustain our nerve cells for a human lifespan is so complicated, that “it's a miracle that as we get older we can think at all,” she jokes. People missing one copy of *p73* will not necessarily suffer from degeneration of their brains, Miller says, but, “we think of it as a susceptibility factor for neurodegeneration or injury.”