Model for angelman syndrome developed

August 14 2008

A model for studying the genetics of Angelman syndrome, a neurological disorder that causes mental retardation and other symptoms in one out of 15,000 births, has been developed by biologists at The University of Texas at Austin.

Their research demonstrates that when a particular fruit fly gene, dube3a, is altered, the mutant flies show behavioral dysfunctions similar to those experienced by humans whose UBE3A gene doesn't function normally.

The work, led by Yaning Wu and Janice Fischer of the Section of Molecular Cell and Developmental Biology, is described in *PNAS Early Edition* online this week (Aug. 11-15), and will appear in the print version of the Proceedings of the National Academy of Sciences later this month.

"People inherit Angelman syndrome as a mutant UBE3A gene that does not make UBE3A protein," says Fischer, a professor in the Institute for Cellular and Molecular Biology.

The UBE3A protein is an enzyme that attaches a small protein called ubiquitin to other proteins. Ubiquitin attachment signals that the tagged protein needs to be degraded.

"The simplest explanation for the disease biochemistry is that when UBE3A is not around to do its job, its substrates aren't being degraded like they should be, and these proteins build up and interfere with brain

functions," Fischer says.

The symptoms of Angelman syndrome in humans include severe mental retardation, epileptic seizures and sleep disturbances.

The work Wu, Fischer and their collaborators have done over the last six years has involved engineering fruit flies with the appropriate mutations in their genes and also particular control transgenes.

The researchers ran the mutant flies through a series of tests, comparing their performances to control groups of flies whose dube3a genes functioned normally. Among other results, the mutant flies weren't able to climb as well up the sides of plastic containers, weren't as able to form long-term memories (of aversive shocks) and were more likely to display circadian rhythm irregularities.

In other words, the flies, says Fischer, suffer from a kind of Angelman syndrome, and should therefore offer a useful model for understanding the biochemistry of the disorder in humans. In particular, the fly models may provide clues to which specific protein, or proteins, are accumulating in the brain and causing the dysfunction.

"We've known for more than 10 years which gene is at fault, but we haven't known some of the specifics of the process," she says. "Now that we know that the fly gene works pretty much the way that the human one does, we can look for the key substrate in flies, and eventually test likely candidates in mice and see if they're really associated with the disease."

Source: University of Texas at Austin