

MARCH 01, 2007

## Fruitfly Model Mimics Genetic Instability of Human Neurodegenerative Diseases

Researchers have developed a fruitfly model that replicates the genetic instability seen in a variety of neurodegenerative diseases, including spinocerebellar ataxia type 3 (SCA3) and Huntington's disease. The fly model carries the same genetic mutation that affects humans who have SCA3, a disorder that causes them to lose motor coordination.

The researchers believe their model will provide insight into more than 30 additional human diseases, including fragile X syndrome, that are caused by similar genetic mutations. They have already used it to better understand drugs that are now being evaluated for the treatment of these diseases.

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— Nancy M. Bonini

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In an article published March 1, 2007, in *Science Express*, the advanced online publication of the journal *Science*, the researchers say their findings suggest those drugs may confer a therapeutic double whammy—alleviating two effects of the toxic protein that causes neurodegeneration. The research team was led by Howard Hughes Medical Institute researcher Nancy Bonini and colleague Joonil Jung, who are both at the University of Pennsylvania.

SCA3 and Huntington's disease arise when mutations in their respective genes cause the production of an abnormally long number of repeats of three nucleotides, also known as triplet repeats. The length of the genetic stutter of nucleotides can vary in each disease. For this set of diseases, the repeated nucleotide triplet encodes an amino acid called glutamine, and thus leads to a protein with an abnormally long glutamine string. The malformed protein is

toxic to cells and causes neurological degeneration.

In SCA3 and similar diseases, the length of this glutamine string can grow or shrink as it is passed down from one generation to the next. This feature of the disease, called repeat instability, has important clinical implications because expansion of repeats causes the disease to arise earlier and with greater severity in successive generations of people who carry the mutation, Bonini explained.

Although researchers had reproduced the protein toxicity of SCA3 and similar disorders in earlier fly models, they have had difficulty reproducing the genetic instability of the disorders. Thus, they have been unable to zero in on a central causative feature of the human disease, thwarting their efforts to understand this aspect of the basic pathological mechanisms.

However, in their *Science* article, Jung and Bonini report that they now can see repeat instability in the fruitfly model of SCA3 because in this set of experiments they directed expression of the gene in germline cells—those associated with eggs and sperm—and saw dramatic instability from generation to generation, said Bonini.

So, even though in most of our experiments the parents had a polyglutamine repeat length of seventy-eight, a percentage of the progeny showed altered repeat lengths—either expansions or contractions, she said. We saw more expansions than contractions, which was exciting because it was the first time we had seen this feature reminiscent of the human disease, she said. So the next question was whether this model could help us understand mechanisms that contribute to this instability.

Bonini said that other researchers had shown that DNA with abnormal repeats tends to attract the cell's DNA repair machinery. This machinery is necessary to maintain the integrity of the genome, but it seems that with these large expansions, repair activity may actually promote rather than prevent the problem, she said. Thus, the researchers knocked out a component of the DNA repair machinery in their fly model, and found that compromising repair did reduce repeat instability from generation to generation.

They also found that a gene called CBP, which is involved in DNA repair pathways and has been implicated in this class of diseases, affects the repeat instability. So, there may be a 'feed-forward' phenomenon in which this toxic protein also causes problems in regulating the integrity of the DNA in the repeat, leading to further repeat expansion and creating an even longer, more toxic protein, said Bonini.

In a clinically relevant experiment, the researchers found that a drug that counteracts loss of CBP activity in similar disease models sharply reduced repeat instability in the fruitflies. Drugs of this type are already being investigated as potential treatments for these disorders, said Bonini, and the finding suggests that drugs designed to treat toxicity of the pathogenic protein may exert a double whammy. Because the toxicity of the protein also affects the instability of the causative gene, such drugs may have a more global

effect to also protect against repeat expansion, she said.

Although the new fly model has limitations, Bonini believes we have our foot in the door toward not only understanding this aspect of the disease, but also understanding a fundamental process that controls genomic integrity.

The researchers presented further evidence that suggests the fly model of repeat instability in SCA3 could be applied to other triplet repeat diseases. The same germline-related repeat instability appeared when they tested genes in the fly for Huntington's disease and fragile X disease. Those findings show that what we are seeing with this repeat instability in the fly is not special to our particular transgene or the particular site in the genome, said Bonini. Other triplet repeat transgenes show a similar phenomenon, meaning that these fly models promise to reveal insight into this fundamental property of these diseases, she said.