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FOR HUNTINGTON'S DISEASE CLUES, SCIENTISTS ARE LOOKING IN FRUIT FLIES

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A male common fruit fly (*Drosophila melanogaster*), about 2 mm long, is seen sitting on a blade of grass. | Photo Credit: Getty Images/iStockphoto

Every month, the medical genetics clinic in the Nizam's Institute of Medical Sciences, Hyderabad, sees about three to four people with Huntington's disease. The numbers might appear small, but in each case behind the individual lies a family devastated.

At first, Huntington's disease patients have mild symptoms: forgetfulness, loss of balance, and clumsiness in performing simple tasks. The symptoms begin in the ages 30-50, by when the patient might also have had children. The condition progressively worsens. The patient suffers mood swings, has difficulty in reasoning, shows abnormal and uncontrollable jerky movements, and experiences difficulty in speaking, swallowing, and walking.

The patient eventually dies, but not before raising the spectre that one or more of their children will suffer the same fate. There is no cure.

This is why understanding how Huntington's disease progresses at the molecular level is important, so that it can reveal some mechanism that, if interrupted, can stop the disease in its tracks.

A paper published this month in *Scientific Reports*, by researchers from the University of Szeged, in Hungary, has taken some important strides in this direction based on – surprisingly – the diminutive fruit fly.

The patient's misfortune is that they carry a mutated version of a gene called HTT. The HTT gene codes for a protein called huntingtin, or Htt.

Nerve cells in the human body require the Htt protein for their normal functioning and survival. The mutated gene, however, encodes an abnormal Htt protein that instead destroys the neurons that regulate movement, thinking, and memory.

The normal HTT gene contains a stretch of DNA that specifies the number of times the amino acid glutamine is repeated in the Htt protein. This number varies from 11 to 31. In the mutant versions of the HTT gene, this stretch is expanded to encode 35 or more repeats. Researchers

have even found variants with more than 150 repeats.

As the number of repetitions increase, the severity of Huntington's disease increases and its debilitation begins at an earlier age.

Each one of us has two copies of the HTT gene: one we inherited from the father and one from the mother. The disease is triggered even if only one copy of the gene is mutated while the other is normal. That is, the mutant gene is said to be *dominant* to its normal counterpart.

Some proteins other than Htt also have tracts of multiple glutamines. In a subset of these proteins, the DNA sequence that encodes the tract is larger in mutated versions of the gene. And as in Huntington's disease, these mutants also can cause region-specific neuronal degeneration in the brain that leads to muscle control disorders, like spinocerebellar ataxia.

There are many enzymes that can cut up proteins that have polyglutamine tracts to create shorter fragments containing the polyglutamines. These fragments are toxic because they interfere adversely with several cellular processes.

Different neurons have exhibited a graded sensitivity to these fragments depending on the protein.

In sum, genes with polyglutamine tracts are (potentially) bad news. And we neither know why some of these genes are expanded nor how exactly the short fragments cause neuronal degeneration.

In the new study from Hungary, the researchers genetically engineered fruit flies (*Drosophila melanogaster*) to express the polyglutamine tract of a mutated human HTTgene in their nervous system.

To do this, they used a gene called Gal4 from baker's yeast (*Saccharomyces cerevisiae*). Gal4 contains information with which cells manufacture a protein called Gal4p. This protein binds specifically to a short DNA sequence called the upstream activating sequence (UAS). In baker's yeast, when Gal4p binds to UAS, it activates the expression of all the genes that come *after* (i.e. downstream), allowing the yeast to utilise the sugar galactose.

Remarkably, the Gal4/UAS system also works in the fruit fly genome. When the DNA sequence for the Gal4p protein is placed downstream of a fly gene called *elav*, something curious happens: the Gal4p protein is expressed in all of the fly's neurons – and only in the neurons.

If the fly also carries the mutated HTT gene downstream of UAS, then the fly's neuronal cells make the bad Htt protein, with its polyglutamine tract. Again, these proteins are made only in the neurons.

In this way, the researchers were able to modify fruit flies so that their neurons produced Htt proteins that had 120 repeating units of glutamine. These flies displayed neuronal degeneration, an impaired ability to climb surfaces, and lower viability as well as longevity.

The researchers also had a 'control' group, with fruit flies whose neurons made proteins with 25 repeating glutamine units – which is in the 'normal' range for human HTT. And these flies were largely unaffected.

In other words, expressing the longer tract produced symptoms in the fruit flies resembling those of Huntington's disease in humans – whereas expressing the shorter tract did not.

With the two groups in hand, the researchers set about testing whether the pathogenesis resembling Huntington's disease in the fruit flies was changed for better or for worse when they turned the expression of different genes up or down.

The team investigated 32 genes and found that excessive expression – or overexpression – of one, called Yod1, removed all of the disease-like effects in the flies, including the neurodegeneration, impediments to motor activity, and lower viability and longevity. The team also found 'control' flies that expressed only the short tracts in the Htt proteins, or which jointly expressed the short tract and the Yod1 gene, also showed no signs of neurodegeneration.

In addition, the overexpression of Yod1 was also found to increase the expression of other genes involved in specific cellular processes. The researchers interpreted this to mean certain cellular processes could be part of a broader response by the fly to the cellular stress caused by the longer tract.

The study's findings are significant. This said, scientists will still need to establish that fruit flies that overexpress the *human* version of the Yod1 gene will also suppress the Huntington's-like pathogenesis. If the human gene has an ameliorative effect in the fly, it will be reasonable to expect its overexpression could ameliorate Huntington's disease in humans, too.

Science aficionados won't be surprised to find we are more likely to figure out how bigger tracts induce neurodegeneration from studies with fruit flies than with Huntington's disease patients in the clinic or with postmortem brains. Model systems such as fruit flies and yeasts offer scientists unparalleled versatility with which to investigate questions of the molecular mechanisms triggered by disease genes.

As the saying goes, it takes a village to raise a child. Given studies with yeast and fruit flies have revealed a potentially helpful role for a fly protein in Huntington's disease, these and other model creatures – and the scientists who study them – deserve to be counted among the residents of this village.

The author is a retired scientist.