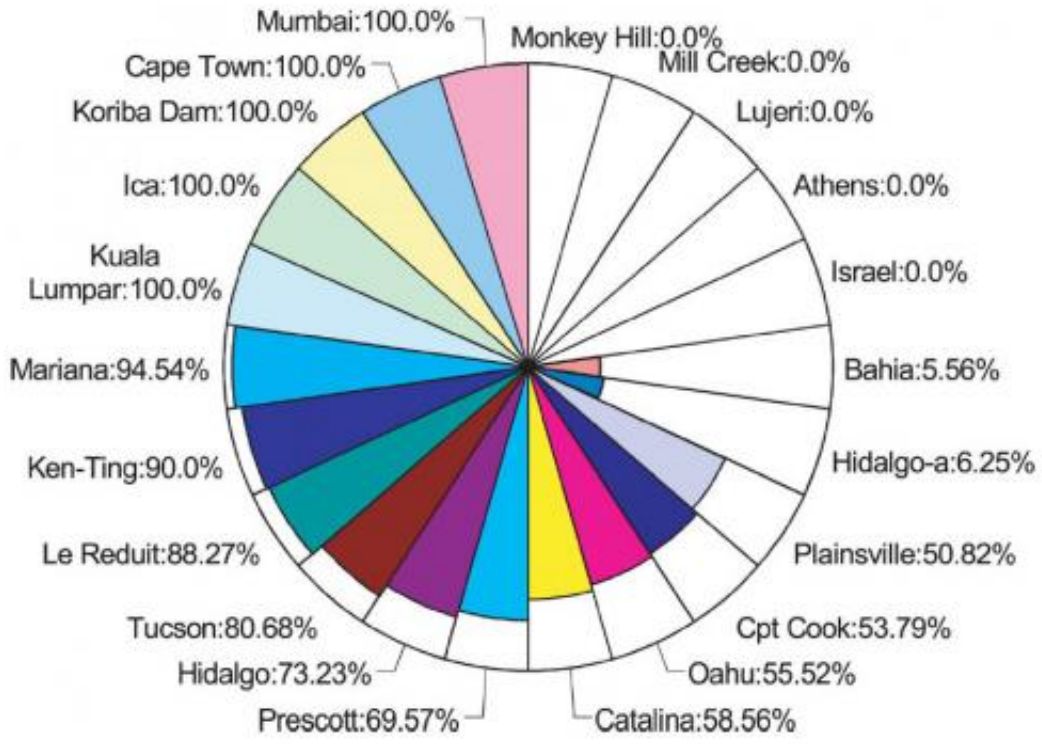
Longevity mutation found in flies far and wide

February 5 2014



Each slice of the pie chart represents a line of fruit flies with a different geographic origin. The colored area in each represents the frequency of Hoppel allele in that line. Flies with the Hoppel transposon lived considerably longer than flies without. Credit: Helfand and Reenan, Brown University

For years, researchers have been investigating how mutations of a gene called Indy (for "I'm Not Dead Yet") affect metabolism, life span, and

reproductive fitness in both mammals and fruit flies. So far mutations in Indy have been studied experimentally only in the lab. No longer. A new study reports that a particularly important variation of the gene with much the same life-governing consequences has actually been widespread among fruit flies, judging by lines gathered from the wild across the entire globe for 60 years.

The naturally occurring variation is the insertion of a transposable element – an invasive snippet of DNA – at a specific position on Indy. Researchers, including Brown University biology professors Dr. Stephen Helfand and Robert Reenan, found that the transposable element, called Hoppel, was present to varying extents in 17 of 22 fruit fly lines gathered from all over the world as far back as the middle of last century. Hoppel was present in 100 percent of a captive fly line started in 2006 in Mumbai, India, for example, and 55 percent of flies descended from those gathered in Oahu, Hawaii, in 1955.

Helfand recalled that in 2000 when he first published a paper in *Science* demonstrating the effect of Indy on life span, a couple of reporters asked him why a mutation that conveyed such advantages wasn't found in the wild.

Indeed, 14 years later the prevalence of Hoppel insertion suggests that it has been beneficial to flies in the wild and therefore persisted during their evolution, said Helfand, of Brown's Department of Molecular Biology, Cellular Biology, and Biochemistry.

"It's kind of remarkable that just the Hoppel in Indy should affect fertility and life span because these flies from around the world are from such differing genetic backgrounds," said Helfand. "This suggests that we are correct that Indy does play a role in longevity. If it does it in the lab, that's great, but now we can show that it does it in the wild."

In the study, published online Jan. 31 in the journal *Aging*, the researchers, led by postdoctoral scholar Chen-Tseh Zhu, describe experiments that confirm that the Hoppel transposon's presence positively affected life span and fertility in the flies. What they found is that the optimal case for those two traits was heterozygosity: one allele, or copy, of the Indy gene in a fly having the insertion and the other not having it.

Life span and fertility

The researchers measured the physiological effects of Hoppel by looking at flies from three different lines: one from Oahu gathered in 1950s, another from Captain Cook, Hawaii, gathered in 2007, and one with its origin in Hidalgo, Mexico, in 2005. Each line had some flies with at least one copy of Indy with Hoppel and some with no Hoppel in Indy.

The heterozygous females in these lines ended up laying about 10 percent more eggs than flies that had no Indy alleles with Hoppel. Flies for whom both Indy alleles had Hoppel laid the fewest eggs. This demonstrates that one Indy allele with Hoppel had a strong selective advantage in reproductive fitness, Helfand said.

For life span, flies that had Hoppel on at least one Indy allele lived considerably longer than flies with no Hoppel on either chromosome. For example, among one group of females, by day 60, more than 80 percent of heterozygotes, and about 80 percent with Hoppel on both alleles were still alive. For those without any Hoppel insertion, less than 60 percent were still buzzing about by day 60.

Indy and Hoppel

For all the prior lab work, researchers are still not completely sure how

Indy works, with our without mutations such as the Hoppel insertion. The protein the gene encodes appears to help gate metabolically important small nutrients such as citrate in the cell cytoplasm. Mutations in the gene appear to affect the concentration of these nutrients in the cell, effectively mimicking the effect of living on a calorie-restricted diet. Calorie restriction and certain Indy mutations have been shown to extend life span in flies and nematodes.

The hypothesis the scientists pursued is that mutations in Indy regulate the expression of the normal Indy gene, thereby leading to changes in the level of Indy activity in the body for better or worse. For that reason, the researchers measured levels of mRNA (the molecular means by which genes are expressed) in the flies. The more Hoppel insertion there was, they found, the more Indy expression there was. Heterozygotes lived longest and laid the most eggs, suggesting that the best level of expression might be the moderate one.

That the transposable element appears to confer benefits is a very exciting finding, Helfand said.

"It has often been suggested that the insertion of transposable elements into genes are largely detrimental to the organism," he said. "The present study is one of the few documented cases demonstrating insertion of a transposable element to have a positive benefit for the organism. Furthermore, it suggests that mutations due to transposable element insertion into genes may represent one of the ways by which new genetic material is produced, providing the raw material for natural selection and adaptive evolution."

Provided by Brown University