Life-history traits may affect DNA mutation rates in males more than in females

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A composite image of 4 of the 32 mammal species whose life-history traits and DNA mutation rates are studied in the Penn State University laboratory of Kateryna Makova. From the top left corner, moving clockwise: a wild dog, a hyrax, a bat, and an elephant. Individual images are online at http://www.science.psu.edu/news-and-events/2011-news/Makova6-2011. Credit: Anton Nekrutenko, Makova lab, Penn State University

For the first time, scientists have used large-scale DNA sequencing data to investigate a long-standing evolutionary assumption: DNA mutation rates are influenced by a set of species-specific life-history traits. These traits include metabolic rate and the interval of time between an individual's birth and the birth of its offspring, known as generation time. The team of researchers led by Kateryna Makova, a Penn State University associate professor of biology, and first author Melissa

Wilson Sayres, a graduate student, used whole-genome sequence data to test life-history hypotheses for 32 mammalian species, including humans. For each species, they studied the mutation rate, estimated by the rate of substitutions in neutrally evolving DNA segments -- chunks of genetic material that are not subject to natural selection. They then correlated their estimations with several indicators of life history. The results of the research will be published in the journal *Evolution* on 13 June 2011.

One of the many implications of this research is that life-history traits of extinct species now could be discoverable. "Correlations between life-history traits and mutation rates for existing species make it possible to develop a hypothesis in reverse for an ancient species for which we have genomic data, but no living individuals to observe as test subjects," Makova explained. "So, if we have information about how extant species' life history affects mutation rates, it becomes possible to make inferences about the life history of a species that has been extinct for even tens of thousands of years, simply by looking at the genomic data."

To find correlations between life history and mutation rates, the scientists first focused on generation time. "The expected relationship between generation time and mutation rate is quite simple and intuitive," Makova said. "The more generations a species has per unit of time, the more chances there are for something to go wrong; that is, for mutations or changes in the DNA sequence to occur." Makova explained that the difference between mice and humans could be used to illustrate how vastly generation time can vary from species to species. On the one hand, mice in the wild usually have their first litter at just six months of age, and thus their generation time is very short. Humans, on the other hand, have offspring when they are at least in their mid-teens or even in their twenties, and thus have a longer generation time. "If we do the math we see that, for mice, every 100 years equates to about 200 generations, whereas for humans, we end up with only five generations

every 100 years," Makova said. After comparing 32 mammalian species, her team found that the strongest, most significant life-history indicator of mutation rate was, in fact, the average time between a species member's birth and the birth of its first offspring, accounting for a healthy 40% of mutation-rate variation among species.

Makova's team also found that generation time affects male mutation bias -- a higher rate of DNA mutation in the male sperm versus the female egg. "Females of a species are born with their entire lifetime supply of oocytes, or egg cells. These cells have to divide only once to become fertilizable," Makova explained. "However, males of a species produce sperm throughout their reproductive life, and, compared with egg cells, sperm cells undergo many more DNA replications -- many more chances for mutations to occur." Previous researchers had demonstrated a higher DNA mutation rate in mammalian males than in mammalian females, a phenomenon called male mutation bias. However, until now, no one had shown that generation time was the main determinant of this phenomenon.

The second life-history trait that Makova's team examined was metabolic rate -- the amount of energy expended by an animal daily -- and how it correlates with genetic mutations. Wilson Sayres explained that some of the team's 32 test species, such as shrews and rodents, fell into the high-metabolism category, while others, such as dolphins and elephants, fell into the low-metabolism category. Previous researchers had hypothesized that the higher the metabolic rate, the greater the number of mutations. "According to this idea, sperm cells should be more affected than egg cells by a higher metabolic rate," Wilson Sayres said. "A sperm cell is very active and constantly moving, and, in addition, its cell membrane is not very dense. But an egg cell basically sits there and does nothing, while being protected by a thicker membrane, much like a coat of armor." Wilson Sayres explained that the combination of high energy and meager protection leaves sperm cells

more susceptible to bombardment by free radicals -- atoms or molecules with unpaired electrons -- and that these free radicals can increase mutations. "The hypothesis is that a high metabolism greatly increases this already volatile situation, especially for sperm; so, in our study, we expected stronger male mutation bias in organisms with high metabolic rate," Wilson Sayres said.

Makova's team found that, unlike generation time, metabolic rate appeared to be only a moderate predictor of mutation rates and of male mutation bias. "While this finding was not as significant as the generation-time result, I suspect that further studies may provide stronger evidence that metabolic rate exerts an important influence on mutation rates and male mutation bias," Makova said. She explained that the challenge is to disentangle metabolic rate as a separate factor from generation time. "The two factors strongly correlate with one another, so it's hard to get a clear fix on how metabolism might be acting independently of generation-time intervals."

Third, Makova and her team explored another life-history trait that other researchers had hypothesized might affect mutation rates -- sperm competition. "Sperm competition is just that -- the struggle between the sperm of different males to fertilize egg cells," Wilson Sayres said. "In a species such as the chimpanzee, where females mate with many different males during a given cycle, intense sperm competition results in large testicle size, and thus, high sperm production. But in a harem species such as the gorilla, where each female is basically exclusive to one male, sperm competition is much less relevant, and the result is small testicle size and low sperm production." Makova explained that sperm competition should, in theory, correlate positively with sperm mutation and thus a higher male mutation bias. "The more sperm that are produced, the more cell divisions are needed and the greater the chances are of mistakes during DNA copying, or replication," Makova said.

However, in the case of sperm competition, the results were surprising. "We did not find as strong an association between male mutation bias and sperm competition as other researchers had hypothesized, although we speculate that future studies might yield different results if the data on sperm competition are collected in different ways," Wilson Sayres explained.

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