

UNM researchers study spontaneous mutations with implications across biology

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UNM Associate Professor Vaishali Katju examines a free-living transparent nematode as part of her research on spontaneous mutations. Credit: Vaishali Katju

Researchers at the University of New Mexico in the Department of Biology are studying the rate and fitness effects of spontaneous mutations, a central area of study in evolution and biology. The research, enabled through a three-year, \$750,000 National Science Foundation grant through the Division of Molecular and Cellular Biosciences, will provide researchers with a broad and comprehensive understanding of

the evolutionary process with implications across the field of biology including the evolution of complex human disease, drug-resistant bacteria and viruses and cancers.

"Most mutations are harmful," said UNM Associate Professor Vaishali Katju, who is the grant's principal investigator. "They are the ultimate cause of most of our heritable diseases and yet, they also provide the genetic fodder for the origin of the wonderful diversity of life we observe all around us. Without mutations, there is no evolution. Before mutation result in differences between species, they exist as variants in populations. In order to understand the probability of the survival and loss of these variants from populations, we need to understand the distribution of the consequences that these mutations have for survival and fecundity, often referred to as fitness in [evolutionary biology](#)."

The probability that a novel mutation is passed on to future generations depends on the effect(s) of the mutation on fitness. But the fate of mutations also depends on the size of the [population](#). In very small populations, chance events can cause harmful mutations to accumulate in genomes. When the population size is 1, the importance of chance is great and mutations that reduce fitness can accumulate readily. In larger populations, the efficiency of [natural selection](#) in removing detrimental mutations from the population is greater and the importance of chance events in determining which mutations accumulate is reduced. The researchers are using these principles to analyze the number and types of mutations that accumulate under varying strengths of natural selection and chance to help them elucidate the distribution of fitness effects of [spontaneous mutations](#).

As part of the study, researchers created spontaneous mutation accumulation (MA) lines using *Caenorhabditis elegans*, a free-living transparent nematode or roundworm species that lives about two weeks and is about one millimeter in size. Although these worms are quite

small, they have almost as many genes in their genomes as humans. The MA lines were evolved in parallel for more than 400 consecutive generations at three different population sizes (1, 10 and 100 individuals per generation).

The advantage of using a simple model organism for studies like these can be seen when the researchers consider that 400 hundred generations in humans would span 8,000 years. The maintenance of the MA lines at 1, 10 and 100 individuals allowed researchers to influence the spectrum of mutations that can accumulate in these populations. When partnered with massively parallel Illumina paired-ends sequencing and Oligonucleotide Array Comparative Genomic Hybridization (oaCGH), the research offers an unprecedented framework that assesses the interaction between mutation and natural selection at the genome-wide scale. In particular, the data will be used to make inferences about the consequences of different types of mutations on fitness.

"The size of this data set is the most ambitious experiment of its kind in any eukaryotic species," Katju said. "With the powerful genomic sequencing currently underway at the University of Washington, the experimental lines will enable unprecedented resolution in the identification of diverse classes of mutation on a genome-wide scale at the mitochondrial and nuclear level, investigate their differential rates of accumulation under varying population sizes and infer the distribution of fitness effects for diverse classes of mutations."

In addition to helping answer fundamental question in evolutionary biology, the results have far reaching implications for fields seemingly as far apart as human health and disease and conservation biology. "Many endangered populations are not at risk just due to habitat loss and human encroachment. Due to their small population sizes, harmful mutations have an increased chance of replacing valuable gene variants in populations and this in turn may erode their genetic integrity. This in

turn may hasten the demise of many species," said Katju.

In addition to the molecular analyses, the populations will be assayed at regular time-intervals to quantify the rate of fitness decay at different population sizes. This will determine the extent to which populations maintained at larger size are buffered from mutational degradation.

C. elegans has many traits that are valuable for experimental evolution studies such as this one, including the ability to self-fertilize and a short generation time. In addition, the experimental populations can be frozen and resurrected for additional future analysis. This makes it possible to discover when particular mutations occurred.

"One hypothesis regarding the evolution of mutation rates is that organisms with low fitness due to deleterious mutations will mutate more frequently. The ability to resurrect and analyze past generations will be used to test this particular hypothesis," said Katju.

With a unified account of evolution at the genetic and phenotypic levels, the research will yield significant insights into the evolutionary process at multiple, fundamental scales - the genetic basis of variation, the evolutionary dynamics of [mutations](#) under the forces of natural selection and genetic drift (chance events), and their range of fitness effects.

"The interface of molecular evolution with genome-wide analyses and phenotypic data has the potential to yield major scientific advances," said Katju. By training one postdoctoral fellow, two graduate students, and undergraduate student researchers in the conceptual and technical foundations of these subfields, this project will contribute significantly to building interdisciplinary expertise in these areas.

Additional educational and outreach activities such as public seminars and panel discussions involving the general public and local high school

students will aim to foster evolutionary thought and insights within a state comprised of a large number of under-represented minorities.

To view the abstract, visit: [The Molecular and Fitness Consequences of Spontaneous Mutation](#).

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Provided by University of New Mexico

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