New insights on link between genetic mutations and biological evolution

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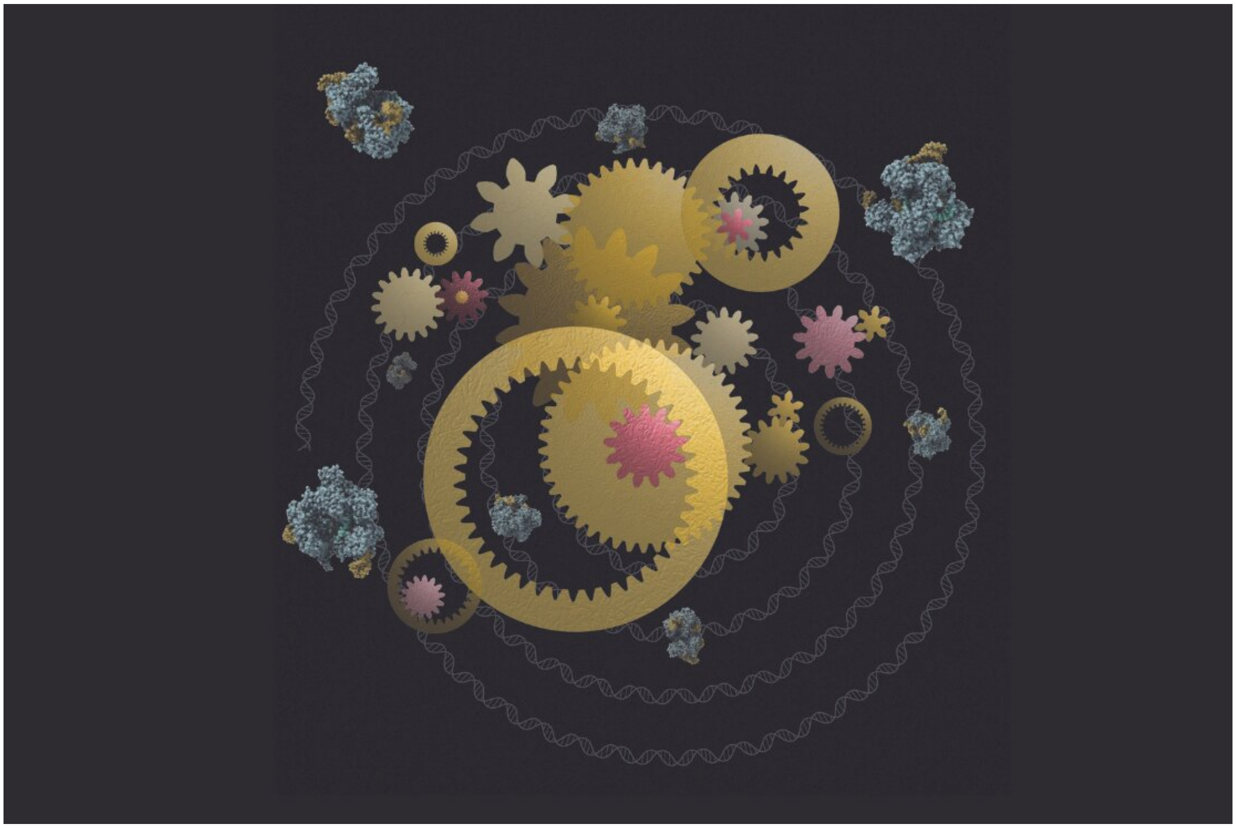

Abstraction of experimentation carried out by UTM biologist Alex N. Nguyen Ba. Credit: University of Toronto Mississauga

In biological evolution, we know that it's all about the survival of the fittest: organisms that develop genetic traits that allow them to better adapt to their physical environment are more likely to thrive, and thus pass down their winning genes to their offspring.

From the longer-beaked Galapagos Island finches studied by biologist Charles Darwin that enabled them to more effectively snatch insects, to the ability of some humans over others to digest milk, the process of natural selection results in genetic differences that give some organisms an edge over others.

New research by University of Toronto Mississauga biology assistant professor Alex N. Nguyen Ba adds an important dimension to our understanding of how genes interact in the evolutionary process.

Nguyen Ba is the co-principal investigator behind a study published this month in the journal *Science*. The first-of-its-kind study shows that different combinations of genetic mutations can have an impact on the evolutionary process—a finding that could benefit areas such as personalized medicine and vaccine design.

"Evolution is a force that drives all of life on this planet," Nguyen Ba says. "Understanding how much we can predict about adaptation has been of strong interest to many people in the field."

Adaptation can be compared to climbing a mountain. The paths taken to the various possible peaks are thought to due to successive mutations, and irregularities in the terrain can be attributed to the specific combinations of mutations acquired along the way. But how can scientists predict the route to the mountain top?

"There are huge implications if we can figure out what's going to happen in the future for living organisms," says Nguyen Ba.

At UTM's annb lab, Nguyen Ba and his team of researchers explore genetic mutations in cells and their impact on evolution using next-generation technologies. These include high-throughput synthetic biology—designing new biological systems or changing existing ones for research purposes—and a desk-sized robot that can process numerous biological samples.

He started the study five years ago when he was a postdoctoral fellow at Harvard University's Desai Lab. There, he collaborated with Christopher Bakerlee, who is the study's co-principal investigator.

Together, Nguyen Ba and Bakerlee used CRISPR gene-editing technology to alter genes in the cells of yeast, which is commonly used in genetic engineering research because it shares some genes with humans.

They worked with 10 missense mutations, which are aberrations in DNA code that change the production of amino acids. Considered the building blocks of life, amino acids are molecules that combine to form proteins, which conduct everything from healing wounds to providing energy to making antibodies.

The experimentation process involved testing out all possible combinations of these mutations—1,024 in total. The scientists wanted to determine how interactions between genes affect the expression of certain genetic traits.

Nguyen Ba completed the final year of the study at UTM, where he analyzed and interpreted the data. The study revealed that evolution frequently samples combinations of gene mutations with negative synergy between them. This acts on the yeast's evolutionary potential in negative ways, for example, by slowing their rate of adaptation.

The findings run counter to the dogma that all biological adaptation unfolds in a predictable way due to some unknown biological law.

Instead, combinations of mutations that have accumulated through time dictate the future evolutionary potential of an organism.

Moreover, he says, it challenges the dominant view in genetic research that we should study one gene mutation at a time. Examining mutations in combination could help us understand diseases and lead to more precise medicine.

"We're showing that in order for us to have a full understanding of how genes actually behave," says Nguyen Ba. "The combinations of mutations are likely to be very important."

More information: Christopher W. Bakerlee et al, Idiosyncratic epistasis leads to global fitness–correlated trends, *Science* (2022). DOI: 10.1126/science.abm4774

Provided by University of Toronto Mississauga

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