December 14, 2022

Editorial Office

Proceedings on the National Academy of Sciences USA

Dear Editors,

We are submitting a new manuscript, “Aneuploidy can be an evolutionary detour on the path to adaptation”, by Ilia Kohanoski, Martin Pontz, Orna Dahan, Yitzhak Pilpel, Avihu Yona, and Yoav Ram for potential publication in *PNAS*.

Chromosome aneuploidy is frequently observed as cells evolve and adapt to new conditions. It is commonly documented in cancer and when organisms such as fungi adapt. An additional copy of a chromosome can provide stressed cells with a solution to the stress, e.g., due to increased expression of some of the genes encoded on that chromosome. Yet aneuploidy is a costly adaptation and is therefore evolutionarily unstable. It is often suggested to be replaced by other, more focal, genetic adaptations.

An important contribution to this view is a paper by some of us published in *PNAS* (Yona et al 2012), which reported an evolutionary experiment in which yeast populations adapted to heat stress by first becoming aneuploid, only to later lose the extra chromosome while retaining the heat resistance phenotype. It has been suggested that aneuploidy can therefore serve as an evolutionary “stepping stone”: cells quickly become aneuploid under stress, and then slowly search for a refined mutational solution to the stress; after such a mutational solution is found, they revert back to euploidy due to the intrinsic costs of aneuploidy.

Here, we challenge this view of the adaptive role of aneuploidy. We combine evidence from sequencing data and model-based Bayesian inference of the Yona et al. experiment to show that despite its short-term advantage under stress, aneuploidy can sometimes be an evolutionary “detour” rather than a “stepping stone”. That is, cells that become aneuploid may have less descendants in the long-term compared to cells that remain euploid, and populations that become aneuploid may reach the refined adaptive solution slower than those that remain euploid. We predict that aneuploidy is a “detour” when the mutation supply—the product of population size, mutation rate, and mutational target size—is large. On the other hand, we predict that aneuploidy can be a “stepping stone” when the population size is small, or under stresses with small target size, such as drug treatment. Thus, for the first time, we demonstrate the conditions under which these two adaptive roles of aneuploidy apply.

We believe that our surprising results will interest a wide community of researchers from the fields of microbial evolution and genetics, cancer evolution, emergence. of drug resistance, and evolutionary biology in general, due to the increasing awareness to the importance of aneuploidy and copy number variation to adaptive evolution. Moreover, we feel *PNAS* is the natural home for our manuscript, as it is a continues a study published in *PNAS* in 2012 by some of us.

The following is a list of suggested reviewers, all experts in experimental evolution with fungi:

* Anna Selmecki, University of Minnesota Medical School, [selmecki@umn.edu](mailto:selmecki@umn.edu)
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 Sincerely,

Yoav Ram, PhD

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