Review of: "Mutational selection: fragile sites, replicative stress, and genome evolution"

Shengjun Tan[1]

1 Institute of Zoology

Potential competing interests: No potential competing interests to declare.

In this manuscript, Professor Haig discusses the concept of mutational selection, which is a process wherein mutations occurring in a germline cell lineage are subjected to selection based on their impact on the organism's fitness. This process involves competition between a mutation and its unmutated progenitor, as well as competition among all alleles at a specific locus. Mutational selection is considered a pure and cost-effective form of selection because mutations can be eliminated through the death of a single cell or a small clone of cells. Mutational selection particularly favors mutational frailty, leading to a propensity for common fragile sites to break during replication stress. The manuscript also delves into the stress-test hypothesis, which suggests that genes involved in DNA replication and repair undergo increased stress to assess their capacity to function effectively and maintain their integrity against mutational decay. Overall, this manuscript provides valuable insights into the mechanisms of mutational selection and their implications for genome evolution.

To be honest, I am not an expert in this field, especially when the manuscript contains numerous specialized terms and knowledge from theoretical biology. During my first read, many terms left me perplexed, such as "intranuclear selection" and the "stress-test hypothesis." It felt like a brainstorming session where a wealth of knowledge needed to be supplemented. It was only after reading it a second or even third time that I gradually understood the terminology described by Prof. Haig. I was truly amazed by his ability to seamlessly organize all content within the framework of mutational selection, providing readers with a fresh perspective.

As a newcomer, I have a few relatively naive questions. First and foremost, how can one identify mutational selection? I understand it's a complex process with multiple facets. Is there a way to straightforwardly identify certain genes that are subject to mutational selection? Relatedly, how can experiments be designed to confirm mutational selection?

The second question pertains to the examples provided in the article, such as the sites related to achondroplasic dwarfism and McCune-Albright syndrome, which exhibit germline phenotypes, or the presence of common fragile sites (CFS) in *WWOX* and *BRCA1*. How many types of examples can be found in the human genome that demonstrate mutational selection?

Lastly, it's intriguing that all four examples cited in the article exhibit obvious synonymous constraints. To what extent do such conservative sites exist in the genome, and how extensively are they influenced by mutational selection? If statistical analyses could be conducted on this aspect, it would provide a more comprehensive understanding.

Regarding the minor comment: "I looked for evidence of synonymous constraint in the immediate neighborhood of

mutations known to be subject to strong mutational selection causing achondroplasic dwarfism and McCune–Albright syndrome. I looked for evidence of synonymous constraint in the immediate neighborhood of two mutations known to be subject to strong mutational selection." These two sentences do seem redundant.