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

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Potential competing interests: No potential competing interests to declare.

In the manuscript, Professor Haig logically discusses the process of mutational selection including the dependence among multiple mutations, the competition between alleles that lead to the selection and elimination of mutant cells, and the mechanisms which cause the mutational selection by repair and replication of genomic DNA. I am not familiar with medical genetics papers, but I was strongly impressed and convinced by the explanation that the process of "mutational selection" was distinguished into the selection at the cellular level and individual selection, and that the competition between alleles for the superiority of mutation is affected by both genetic competence and difficulty. The two examples of actual observed *de novo* mutations, achondroplasic dwarfism and McCune-Albright syndrome, were also very clear. This study will provide very important insights into the diversification of genomic sequences in eukaryotic evolution.

I have some comments on this manuscript as described below.

On pages 3 and 4, the author presented achondroplasic dwarfism and McCune-Albright syndrome as examples of *de novo* mutations, and showed that the former was growth dominant on male germ cells and the latter was lethal in the early embryo. The author also explained that mutations in the genes for them can be retained or eliminated by selection of the cells with the mutation among other cells. However, do the achondroplasic dwarfism and McCune-Albright syndrome not affect individual selection? if they can be interpreted only by mutational selection, the rationale should be clearly explained.

Next, on pages 6, 7, and 8, the synonymous constraints for the FGFR3 and GNAS genes are very interesting phenomena. However, to these phenomena will be generalized for other genes and other genomic regions in the future, more quantitative consideration is required for the strength and effective regions of synonymous constraints for these two genes. How many synonymous substitutions are found in the regions around the aligned regions shown in Fig. 1? Also, for other genes, how long a region without synonymous substitutions is necessary for the determination of synonymous constraints? How many differences between the synonymous mutation rates in the regions with and without synonymous constraints are also necessary?

Throughout the manuscript, more references and figures to provide a basis for interpretations, and explanations of technical terms are needed to support the reader's understanding.

Finally, I found it very interesting to read this manuscript. Thank you for the opportunity to review.