

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

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**Potential competing interests:** No potential competing interests to declare.

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

Overall, I enjoyed the manuscript, which contains important insights and describes interesting hypotheses. At first sight, however, the content seemed to me a bit of a mixed bag, but after careful reading, it all fits around the topic of natural selection, with the emphasis of mutational selection in the germline, and how this may affect evolution and be in conflict with individual selection. I have some suggestions, mostly about the structure, and about clarification of topics. My main recommendation is to provide both in the abstract and in the introduction more information on what is to be expected in the rest of the manuscript. Additionally, I would like to have more emphasis on the main hypothesis presented in the manuscript, the evolution of mutational frailty due to soft selection in the germline, preferably illustrated with a figure similar to the one in Archetti (2009).

Furthermore, it would be good to have some hierarchy, with main section and subsections, rather than just separate sections at the same level as in the current structure. For example, the mutational stress test hypothesis is a further elaboration of the previous section on elite alleles. Also some sections contain potential examples of hypotheses proposed. Finally, one or two conceptual schematic figures would be helpful for the more visually oriented reader. Below I provide some details.

The current structure is as follows:

1. Abstract. I am not sure of the format of the journal, but I think the abstract would gain from more background and introduction. It now did raise my interest (so it is functional in that sense), but I had to read the rest of the manuscript to understand the abstract properly.
2. Intro section. First mention and intuitive explanation of almost all topics that are later worked out in more detail: distinction between germline segregation and germline mutation, and definition of mutational selection. Introducing the idea of selection for frailty and dominance. Difference between preferred dominance for germline effects and recessiveness for somatic effects. I would recommend to provide more background to start with and to announce what is going to come.
  1. Page 3, 1<sup>st</sup> and 2<sup>nd</sup> paragraph: The author argues that genes favoured by mutational selection exclude their own mutants from subsequent germlines, and to achieve this efficiently, such mutants must have dominant-negative effects. Subsequently, arguments are given for selection for increased dominance, either cis and trans regulated. I

was struggling a bit with the shift of dominance of mutant alleles to dominance of the resident allele, since I erroneously first assumed that it was about dominance of the mutant relative to the resident allele. A schematic figure at the start of the manuscript would help the average reader, I think.

2. In the fifth paragraph, it may be useful to specify that you assume a symmetrical germ-cell division, i.e. both daughter cells will continue to be stem cells, and not an asymmetrical germ-cell division, where one daughter cell remains a germ cell and the other differentiates into somatic tissue or stops to divide.
3. Mutational selection and the frequency of de novo mutations. Two examples, one disease mutation (achondroplasia) that is positively selected within the germline, and one that is negatively selected, but can occur due to somatic mutation (McCune-Albright syndrome). This section ends with a hint to fragile germline phenotypes (next section).
  1. On page 4, the author argues that deleterious mutations favoured by mutational selection increase the genetic load for such mutations, and next that “A further consequence is that mutational selection alters the frequency of mutations at mutation-selection equilibrium”. I would rather consider the increased genetic load as a direct consequence of the increased mutant-allele frequency. As it is formulated now it seems two separate phenomena.
4. The evolution of fragile germline phenotypes. The opposing effects on frailty of mutational selection and recombination. The different effects of mutational selection (favouring frailty) and individual selection (favouring robustness).
  1. A figure similar to the one in Archetti (2009) showing why mutational selection favours frailty, and that for that reproductive compensation, and so ‘soft selection’ has to be assumed will be very helpful.
5. Synonymous constraints. Synonymous constraints may suggest that the nucleic acid phenotype is subject to either individual or mutational selection. I found this section hard to reconcile with the rest of the manuscript. The final paragraph hints to a connection with the rest of the manuscript, but I would like to have a better explanation for the rationale of this idea.
6. Competition for dominance by elite alleles. Quantitative analysis of the idea introduced in the first section.
7. Mutational stress tests. Explanation of ‘the guild’, the consortium of the genes involved in transcription, replication and repair; how selective processes favouring increased difficulty increase the costs of mutation, thus increased selection for reduced mutation rates. Basically, this section is an extension of the previous section.
8. The unsettling effects of repetitive elements. Falls a bit outside the core of the manuscript. This section discusses a complication of mutational selection arising from multi-copy sequences.
9. Fragile sites. Two potential examples of the stress test hypothesis.
10. Conclusions.