

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

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Potential competing interests: No potential competing interests to declare.

As is typical when reading a paper by this author, I learned a lot of biology (some of which I should have already known), was dazzled by the scholarship in diverse fields, and found the ideas very creative. I was hooked from the opening line! Highly recommended for publication in Qeios.

I struggled with the section "Competition for dominance by elite alleles." The exam metaphor is elegant in a literary sense, but many of us will find these ideas more transparent if they are also expressed in conventional terms (*e.g.* probabilities and fitness).

There are connections to other concepts and research themes that would be well to develop:

- One is Eigen's (1971) "error threshold" idea and the related notion of "survival of the flattest" (Wilke 2001).
- In several spots (*e.g.* the section on fragile sites), the author's argument strikes me as a form of group selection. If the author agrees, he might comment on that.
- The interactions between genes discussed in "The evolution of fragile germline phenotypes" have parallels with Dobzhansky-Muller incompatibilities.
- It's nice to see the connection with the enhancer runaway model of Fyøret *al.* (2015). More recent publications by Lenormand and collaborators (*e.g.* 2020) are also relevant and might be cited.

I agree that the data shown regarding conservation of synonymous sites in *FGFR3* (p 7) make a strong case for some form of purifying selection. It would be good bolster this appeal to common sense with some numbers, *e.g.* the average number of synonymous substitutions at other genes.

It's strange that the long discussion of *BRCA1* (p. 14 *et seq.*) makes no mention of its role in cancer, which is certainly relevant to the evolutionary perspective taken in this paper.

Figs 1 & 3: These are difficult to parse for a couple of reasons. It would be helpful to see the codon boundaries. The caption might state how/why the figures show synonymous constraint.

Trivial:

- Many of us who (sadly) are less versed in the nuts and bolts of nucleotide replication would appreciate brief definitions

of several of the less common terms, *e.g.* end-resection.

- P 4, l 7: “Mutational selection occurs only in generations in which a mutation occurs....” Rephrase.
- P 6, ll 14 & 17: “I looked...” is repeated.