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

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Potential competing interests: No potential competing interests to declare.

The author is interested in the role of the genetic structure of the genome as a factor in evolution. This is a unique and important perspective. The current paper makes the general proposal that "genes evolve sequence properties in *cis* that challenge the competence of their own gene products", thereby providing intra-individual selection in favor of their maintenance and against appearance of mutant alleles. This idea, and a number of related suggestions, is placed in the broader structure of what the author calls "mutational selection" which, in brief, is mitotic competition of germline cell lineages that differ because of mutation. In this context, basic cellular functions (replication, transcription, etc) are of primary importance as contrast to the situation when groups of cells are developing coordinately into organism-level features. The multiple ideas presented are all very interesting. The examples provided specifically illustrate and integrate these ideas in a compelling way. They also reflect the author's deep understanding of basic molecular processes and genetic structure.

The only point that made me "blink" slightly was the idea that evolutionary considerations dictate the presence of long segments that encode "intrinsically disordered regions" of proteins. This took some getting used to, but after some thought, makes perfect sense - intrinsically disordered regions are not subject to the same amino acid constraints as other parts of proteins and can also more easily tolerate internally repeated nucleic acid sequences, which play a key role in the author's suggestions. Further exploration of this possibility would be an interesting issue for the future.

Some of the suggestions pertain generally to mutational selection regardless of mechanism; others pertain specifically to the possibility of nucleic acid sequence-based effects. The various points are interwoven conceptually. This is reflected in a somewhat non-linear presentation. While not wishing to derail the author's intellectual path, this reviewer would have appreciated a slightly more organized structure (e.g. to separate features specific to mutational selection, and the relevant examples provided, from differences between mutational and "individual" selection).

All of these suggestions beg the question of how they can be tested more directly, e.g. in an experimentally tractable organism such as budding yeast.