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RECOMMENDATION

Replication-independent mutations: a universal signature?

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Based on reviews by:

Marc Robinson-Rechavi and Robert Lanfear

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A recommendation of

Achaz G, Gangloff S, and Arcangioli B. The quiescent X, the replicative Y and the Autosomes. *bioRxiv* 351288, ver. 3 peer-reviewed and recommended by *PCI Evol Biol* (2019). DOI: 10.1101/351288

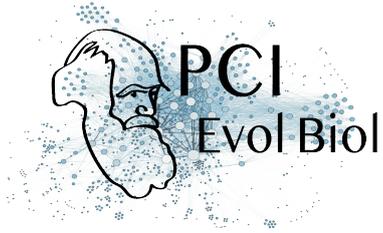
Mutations are the primary source of genetic variation, and there is an obvious interest in characterizing and understanding the processes by which they appear. One particularly important question is the relative abundance, and nature, of replication-dependent and replication-independent mutations - the former arise as cells replicate due to DNA polymerization errors, whereas the latter are unrelated to the cell cycle. A recent experimental study in fission yeast identified a signature of mutations in quiescent (=non-replicating) cells: the spectrum of such mutations is characterized by an enrichment in insertions and deletions (indels) compared to point mutations, and an enrichment of deletions compared to insertions [2].

What Achaz *et al.* [1] report here is that the very same signature is detectable in humans. This time the approach is indirect and relies on two key aspects of mammalian reproduction biology: (1) oocytes remain quiescent over most of a female's lifespan, whereas spermatocytes keep dividing after male puberty, and (2) X chromosome, Y chromosome and autosomes spend different amounts of time in a female vs. male context. In agreement with the yeast study, Achaz *et al.* show that in humans the male-associated Y chromosome, for which quiescence is minimal, has by far the lowest ratios of indels to point mutations and of deletions to insertions, whereas the female-associated X chromosome has the highest. This is true both of variants that are polymorphic among humans and of fixed differences between humans and chimpanzees.

So we appear to be here learning about an important and general aspect of the mutation process. The authors suggest that, to a large extent, chromosomes tend to break in pieces at a rate that is proportional to absolute time - because indels in quiescent stage presumably result

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from double-strand DNA breaks. A very recent analysis of numerous mother-father-child trios in humans confirms this prediction in demonstrating an effect of maternal age, but not of paternal age, on the recombination rate [3]. This result also has important implications with respect to the interpretation of substitution rate variation among taxa and genomic compartments, particularly mitochondrial vs. nuclear, and their relationship with the generation time and longevity of organisms (e.g. [4]).

References

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Appendix

Reviews by Marc Robinson-Rechavi and Robert Lanfear, DOI: 10.24072/pci.evolbiol.100066