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Transition transversion ratio in mtDNA is higher in long-versus short-lived mammalians: effects of ROS and replication?

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Motivation and Aim: Transition/transversion ratio (ts/tv) in animal mtDNAs significantly differs between various taxa; however, no universal explanation has been suggested.
Methods and Algorithms: Using four-fold degenerative synonymous fixations of mammalian mtDNAs here we reconstructed mutation spectrum for more than 300 species. In order to do so we built an original pipeline implemented in Perl and Python. The pipeline intended to build of intraspecies mutation spectra (IMS) for each species under analysis by reconciliation of intraspecies sequences on the basis of ancestral sequence reconstruction (using parsimony and/or ML) in each inner tree nodes. After the IMS building we normalized IMS by genome-wide nucleotide content. This work we analyzed species if it have at least 30 synonymous fixations along intraspecies tree (>300 mammalian species were selected). At the last step we used phylogenetic comparative methods implemented in R for the comparison of the IMS evolution with species generation time (age of the maturation of a female taken from AnAge database).
Results: The average mutation signature is very similar with mutation signature derived from somatic mitochondrial mutations in human cancers: two common types of substitutions (G->A and T->C transitions, light mtDNA strand notations) demonstrating strong strand asymmetry (occurring mainly on a heavy mtDNA strand). Comparing mutation spectra of long- versus short-lived mammals we observed a gradient: species-specific ts/tv increases with generation time and this correlation is robust to numerous potential confounders, such as nucleotide content, phylogenetic inertia and types of analyzed mitochondrial genes.
Conclusion: Our findings might be explained by two, non-mutually exclusive hypotheses (i) short-lived species have increased basal metabolic rate and thus can suffer from the increased burden of ROS, manifesting itself by G:C->T:A transversions; (ii) long-lived species have prolonged replication of mtDNA and thus accumulate more C->T and A->G transitions occurring on single-stranded heavy strand during replication [2]. Our findings are in line with previously observed correlations between mitochondrial nucleotide content and mammalian lifespan [1] and emphasize that at least some of them are driven by purely mutagenic not selective forces.

References

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