A billion-year trend of amino acid substitutions in the mitochondrial genome

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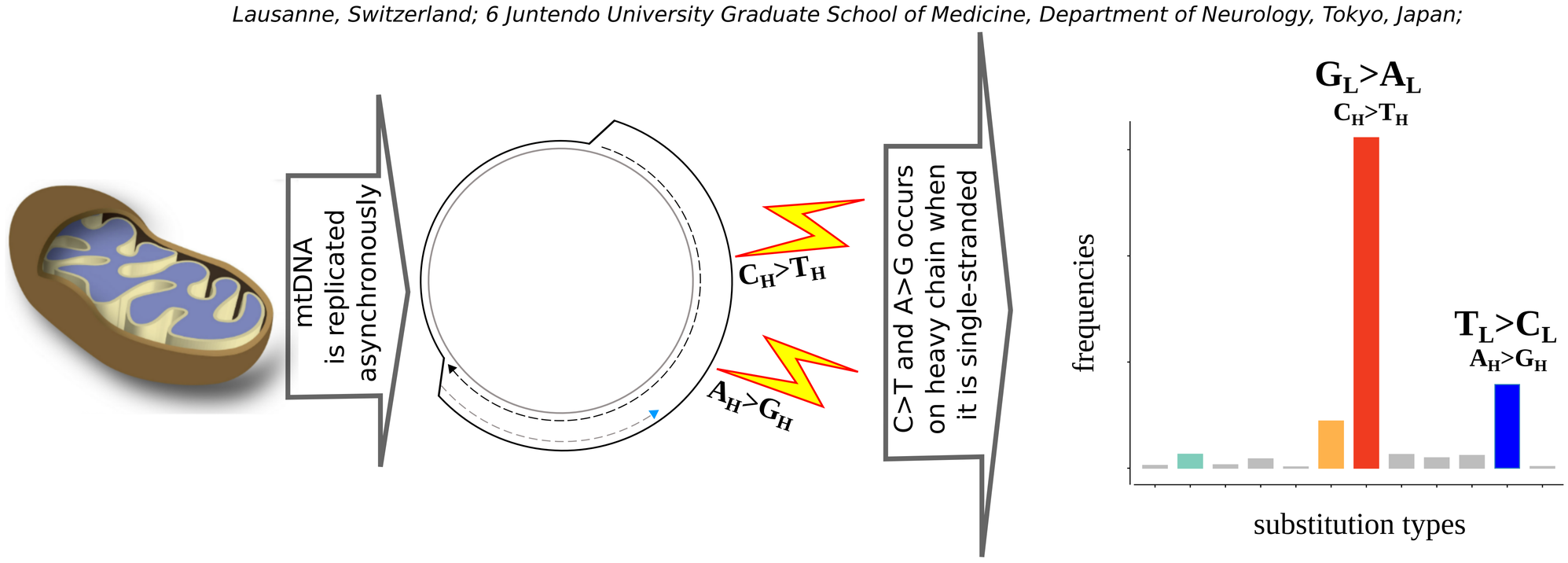
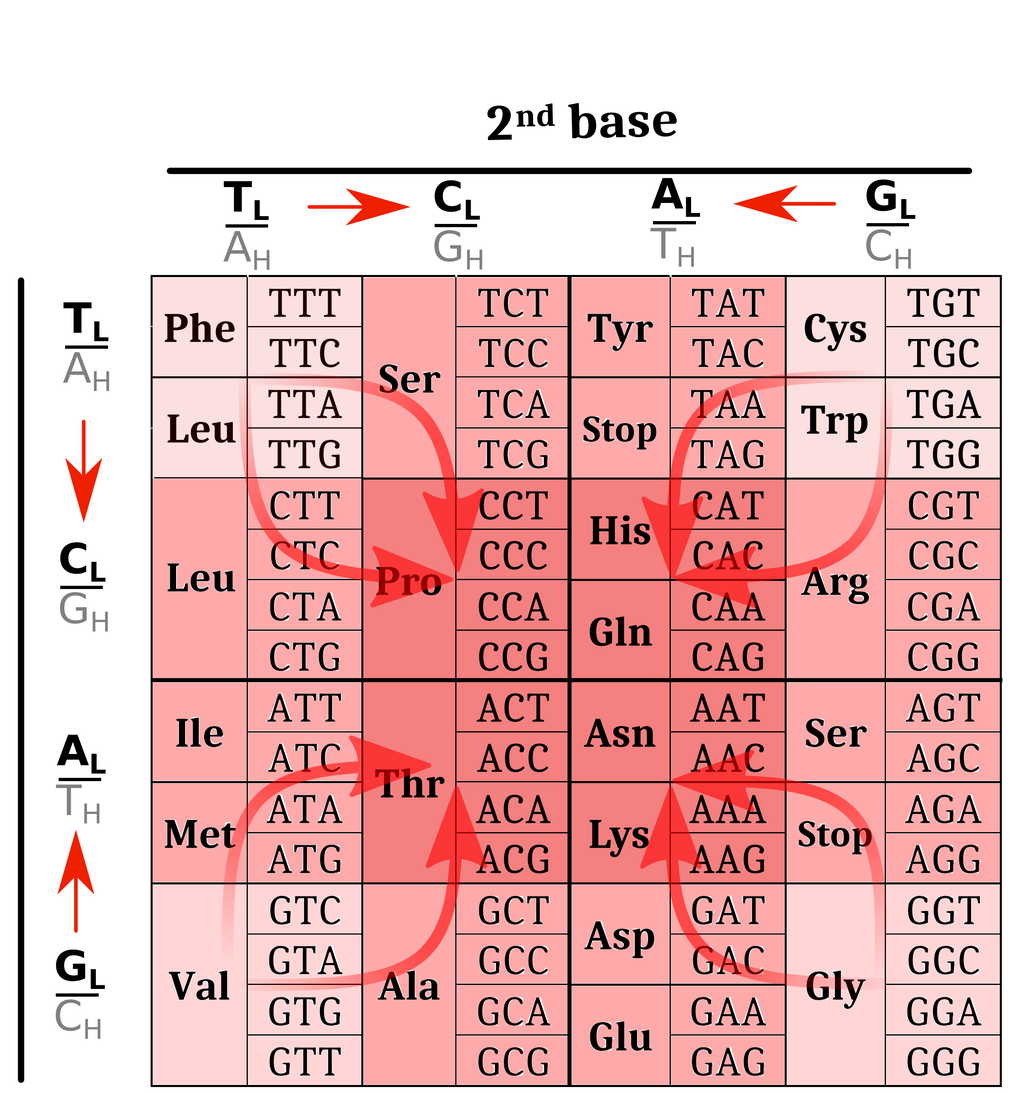
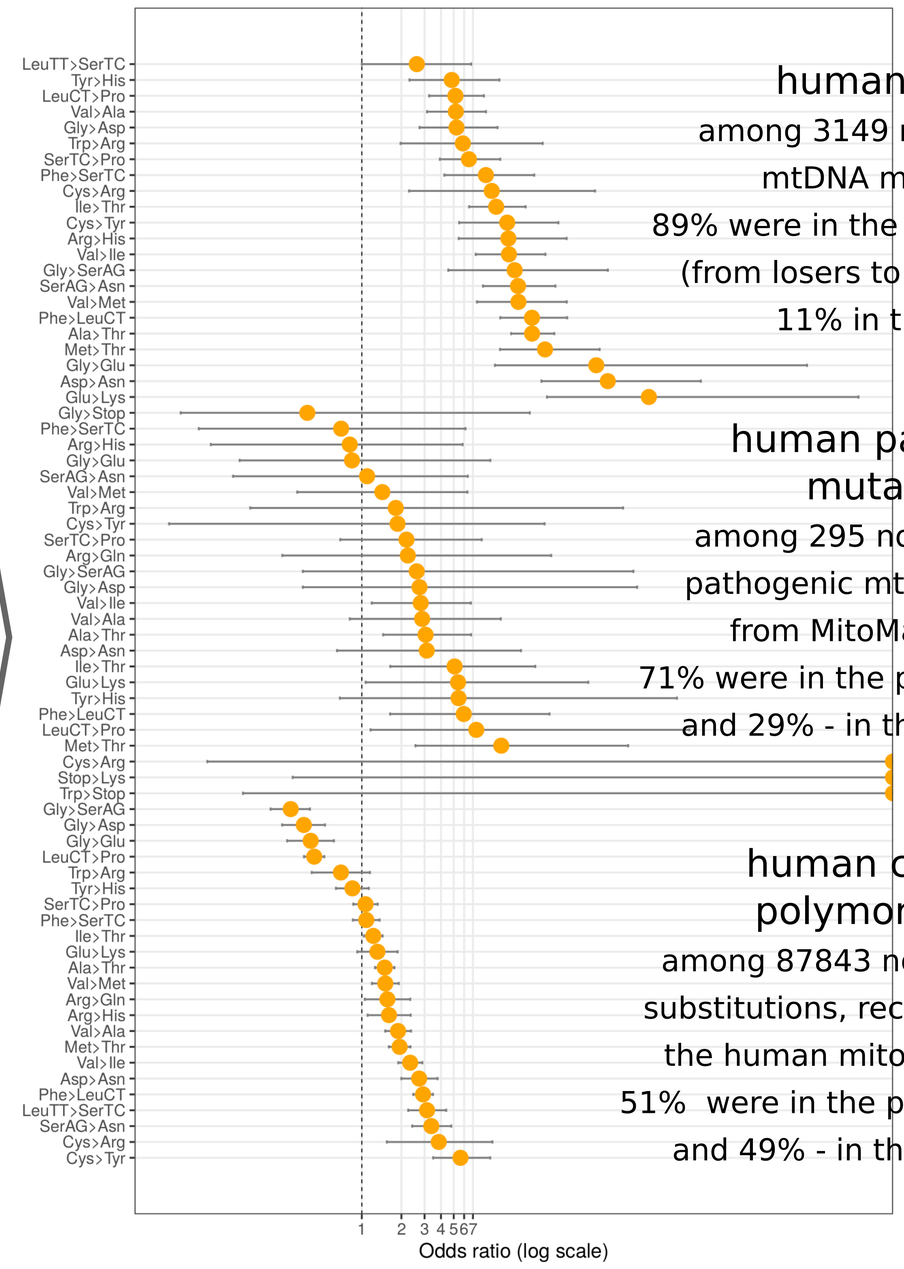


The asymmetrical mutagenesis of mtDNA makes its genome more AC rich and GT poor (L - light chain notation) if selection is weak [1,2]. Indeed, the most common synonymous codons in the human mtDNA are XXA and XXC [3]. Here, we hypothesize further, that not only the codon usage, but also amino-acid usage of mtDNA can be affected by the mutagenesis. We expect that the mutagenesis drives changes from the corners (losers: Phe, Cys, Trp, Gly, Val) to the center (gainers: Pro, His, Gln, Asn, Lys, Thr) of the genetic code:



predicted rate (from losers to gainers) is higher than the opposite (from gainers to losers) in the majority of investigated mtDNA datasets. The trend is more pronounced in datasets with weak selection (somatic mutations in cancers and pathogenic mutations)

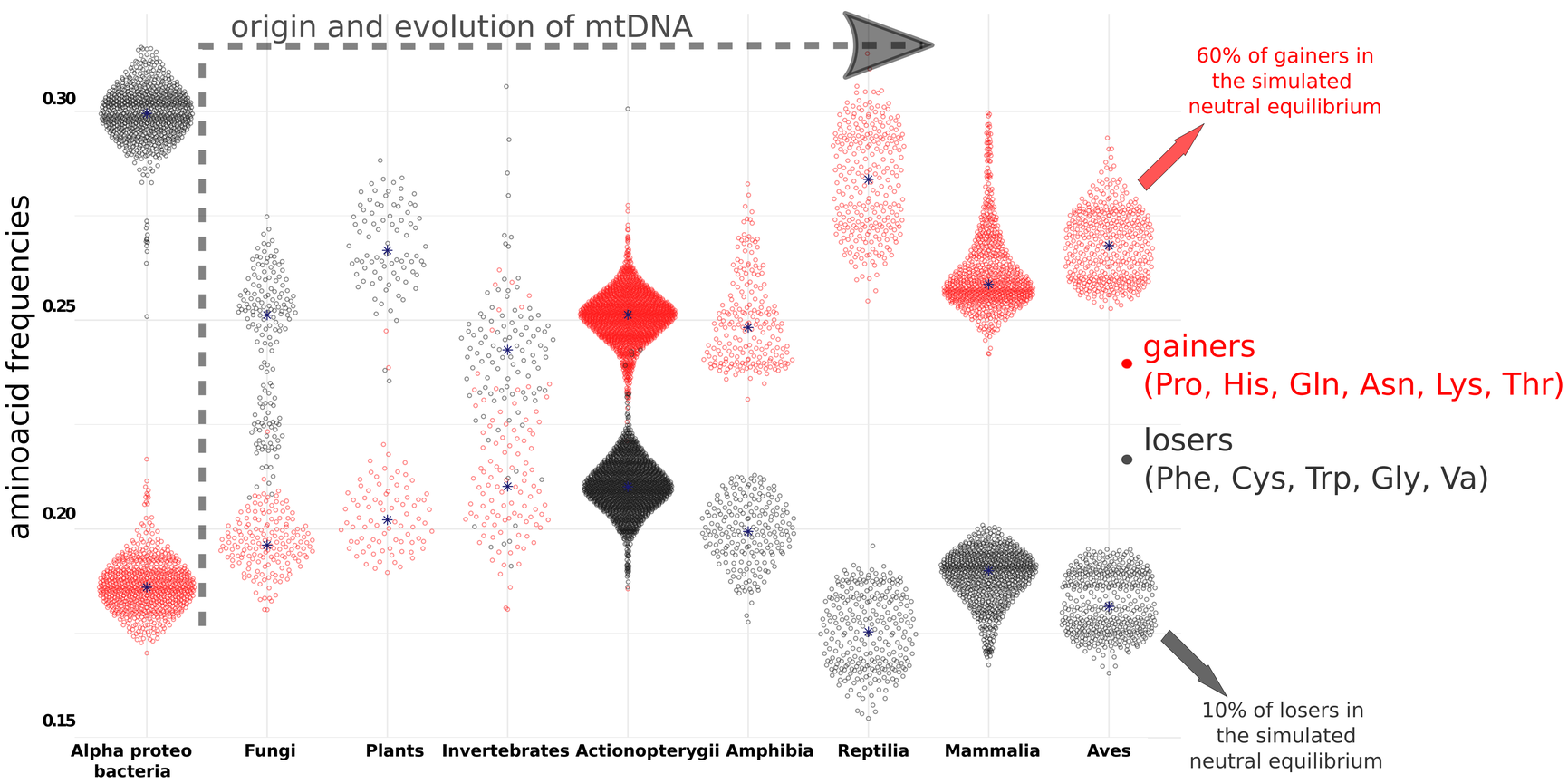


human cancers:
among 3149 nonsynonymous mtDNA mutations [4]
89% were in the predicted direction (from losers to gainers) and only 11% in the opposite

human pathogenic mutations:
among 295 nonsynonymous pathogenic mtDNA mutations from MitoMap database
71% were in the predicted direction and 29% - in the opposite one.

human common polymorphisms:
among 87843 nonsynonymous substitutions, reconstructed from the human mitochondrial tree,
51% were in the predicted direction, and 49% - in the opposite one

Selection is weak in low-sized populations where amino-acid composition can be strongly affected by the mtDNA mutational bias. Comparing frequencies of gainers and losers among taxa with decreasing population size: from bacteria to fungi, plants and invertebrates to vertebrates we demonstrated gradual and longterm increase in gainers and decrease in losers



Altogether we conclude that mtDNA mutational bias, not selection, shapes the global amino-acid composition of the mitochondrial protein-coding genes in the main taxa of eukaryotic species.

REF:

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2 Mikhailova et al. 2020. A mitochondrial mutational signature of temperature and longevity in ectothermic and endothermic vertebrates, BioRxiv.

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4 Yuan et al. 2020. Comprehensive molecular characterization of mitochondrial genomes in human cancers, Nature genetics