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Risk of somatic mitochondrial deletions is affected by the secondary structure of the mitochondrial genome

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Ageing is associated with accumulation of somatic mutations. This process is especially pronounced in mitochondrial genomes (mtDNA) of postmitotic cells, where the accumulation of somatic mitochondrial deletions is associated with healthy ageing and mitochondrial encephalomyopathies. Deletions are often flanked by direct nucleotide repeats, however, they do not provide an exhaustive explanation of deletion distribution. We hypothesized that in parallel with the role of direct repeats there is also a global secondary structure of mtDNA, shaping deletion formation. Analyzing the folding energies of the heavy chain, which stays single-stranded during mtDNA replication, we observed a potential contact zone between 6-9kb and 13-16kb of the major arc of mtDNA. Describing the distribution of deletions in the human mtDNA we demonstrated that the contact zone is 3-times more mutagenic under all else equal. The proposed topological model improves our understanding of the mechanisms of deletion formation in the human mitochondrial genome.