TOWARDS A QUANTITATIVE ASSESSMENT OF THE MITOCHONDRIAL COMPONENT OF AGING: THE FRAGILITY SCORE AS AN INDICATOR OF THE RISK OF MTDNA DELETION FORMATION

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Background: Ageing is often associated with clonal expansion of somatic mitochondrial (mtDNA) deletions, while their origin is still poorly known. Deletions are often flanked by direct nucleotide repeats, however, repeats solely do not provide an exhaustive explanation of deletion distribution. Here, we aim to decipher additional factors affecting formation of mtDNA deletions and create a score for estimation risk of deletion formation.

Materials and methods: Using a collection of human mtDNA deletions and global and local mtDNA properties (distribution of repeats and other structures), we reexamine the risks of somatic mtDNA deletion.

Results: Comparison of the probability of mtDNA deletions in regions flanked by different combinations of direct and inverted repeats reveals that in addition to direct repeats, which are known to influence deletions, there is a strong influence of the secondary structure of single- stranded mtDNA during replication. The secondary structure during replication is formed by inverted repeats, which can form stems and reduce the effective distance between two direct repeats, thereby increasing the probability of deletions.

Conclusion: As we can see, the mitochondrial genome has a specific structure and composition of nucleotides that can influence the formation of deletions. We want to find out how the human mitochondrial anatomy predisposes to deletions.

Regions of mitochondrial DNA have a different risk of deletion, and for each region a metric can be obtained to estimate the probability of deletion based on sequencing data. Nucleotide motifs such as repeats may be associated with a higher risk of deletions in the mitochondrial genome. We are going to study the various features of the global and local structure of mitochondrial genomes (direct and inverted repeats, Gibbs energies, G-quadruplexes, microhomology, rare deletions), primarily in human ones.

By finding fragile places in various human haplogroups, we will be able to create a universal metric for assessing the fragility of regions of the mitochondrial genome.

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Key words: mtDNA, deletions, repeats, secondary structures

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