Point mutations in mitochondrial DNA and their relation with longevity

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Introduction

The idea of how mutations in mitochondrial DNA (mtDNA) define human lifespan has changed over the past few years. Firstly, Mitochondrial Theory of Ageing came up suggesting that an accumulation of mutations in mtDNA reduces mitochondria activity, contributing to ageing process. This model considers all mutations to be detrimental and to reduce longevity, but recent studies suggest that also beneficial mutations can occur throughout life, increasing lifespan.

Objective

The main objective of this work is to summarize the actual state of knowledge of longevity-related mtDNA mutations and how specific point mutations in mtDNA can increase human lifespan.

Material and Methods

In this work, only English-published articles have been selected from NCBI's database; including author manuscripts and review articles.

Several *in silico* analysis have been done in order to understand their molecular effect:

- To compare the folding of a mutated D-loop against a non-mutated, by using the DNA "mfold" web server. D-loop sequence has been taken from human mtDNA L-strand complete sequence, available at GenBank accession number NC_01292.1.
- To study the effect of specific point mutations in mtDNA, by using the the MutPred web server. NADH dehydrogenase 3, NADH dehydrogenase 2 and ATPase subunit 8 coding sequences have been taken from human mtDNA L-strand complete sequence, available at GenBank accession number NC_01292.1.

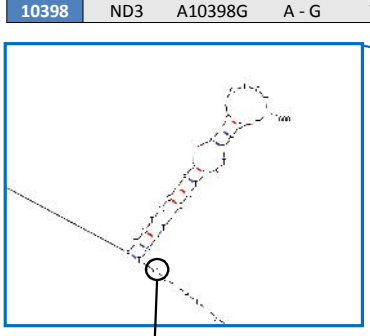
State of the art & Results

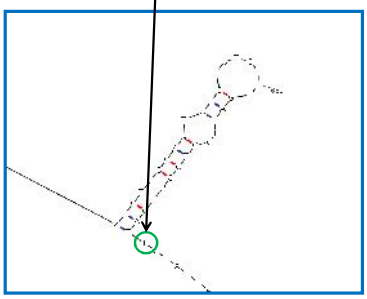
Position	Locus	Allele	Nucleotide	Aminoacid	Possible Effect
146	D-Loop	T146C	T - C	Non-coding	Age-related
150	D-Loop	C150T	C - T	Non-coding	Longevity-related
152	D-Loop	T152C	T - C	Non-coding	Age-related
189	D-Loop	A189G	A - G	Non-coding	Age-related
249	D-Loop	A249G	A - G	Non-coding	Age-related
285	D-Loop	T285C	T - C	Non-coding	Age-related
368	D-Loop	A368G	A - G	Non-coding	Age-related
383	D-Loop	383i	T insertion	Non-coding	Age-related
408	D-Loop	T408A	T - A	Non-coding	Age-related
414	D-Loop	T414G	T - G	Non-coding	Age-related
489	D-Loop	T489C	T - C	Non-coding	Longevity-related
3010	RNR2	G3010A	G – A	-	Longevity-related
5178	ND2	C5178A	C - A	Leu → Met	Longevity-related
8414	ATP8	C8414T	C - T	Leu → Phe	Longevity-related
10398	ND3	A10398G	A - G	Thr → Ala	Longevity-related

mtDNA point mutations are more frequent to be found in the control region than in the coding region. The coding region (D-loop) can be mutated and alter the control of mtDNA replication and transcription. Those mutations related to longevity may improve the efficiency of replication machinery, but the aging-related ones may cause the opposite effect.

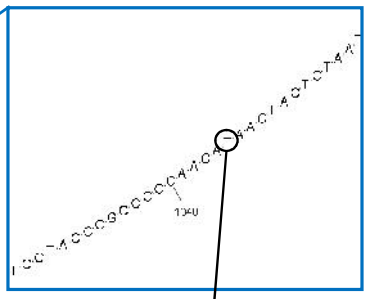
Transition C150T is longevity-related. It was firstly described by Zhang et al. in leukocytes from an overall of 169 Italian individuals. Over the years, this mutation has also been longevity-related in Irish, Finnish and Japanese populations. In some studies with elder individuals this mutation appears to be linked with T489C and A10398G. It has been detected in peripheral blood, granulocytes and fibroblasts.

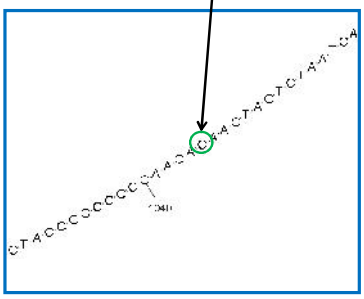
Transversion C5178A is longevity-related. It was firstly detected by Tanaka et al. at 1998 from Japanese in- and out-patients. This mutation takes place within NADH dehydrogenase subunit 2 gen and co-segregates with C8414T transition within the ATP synthase subunit 8 gene and G3010A transition within 16S rRNA gene. Further studies suggest that individuals with 5178A are less susceptible to adult-onset diseases than individuals with 5178C allele.

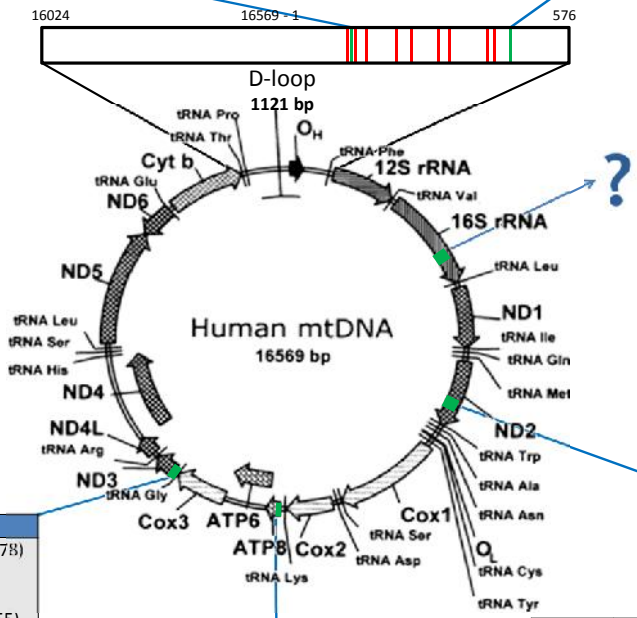




dG = -70.39 Kcal/mol → 150T + 489C → dG = -70.49 Kcal/mol







Mutation	Deleterious	Top 5 features
T114A	0.071	↑ ubiquitination at K236 (P = 0.1278) ↓ disorder (P = 0.2329) ↓ helix (P = 0.2662) ↑ glycosilation at K109 (P = 0.2755) ↓ solvent accessibility (P = 0.4141)

No significant results appeared after analyzing A10398G transition (T114A substitution at NADH dehydrogenase 3).

Mutation	Deleterious	Top 5 features
L17F	0.514	↓ stability (P = 0.1281) ↓ disorder (P = 0.1899) ↑ glycosylation at T14 (P = 0.4295) ↓ MoRF binding (P = 0.4663) ↓ catalytic residues at T14 (P = 0.7037)

C8414T mutation (L17F substitution at ATPase subunit 8), results show this mutation is likely to be deleterious. It probably decreases the activity of ATPase subunit 8 causing a decrease of ROS generation.

Mutation	Deleterious	Top 5 features
L237M	0.099	↓ methylation (P = 0.0463) ↓ helix (P = 0.0558) ↑ ubiquitination at K236 (P = 0.0828) ↑ loop (P = 0.0851) ↑ MoRF binding (P = 0.2194)

C5178A mutation (L237M substitution at NADH dehydrogenase 2), results show a possible loss of methylation at K236 and the gain of molecular recognition features (MoRFs binding). The lack of methylation may increase the activity of NADH dehydrogenase 2 , representing an advantage for the individual.

Conclusions

Over the last years, several articles have reported mtDNA mutations to be over-expressed in centenarians but then, no further investigations are made. In order to make progress in this field, more investigations should be done analyzing several populations and different age groups as delving into the molecular mechanism of each mutation to know the real effect.

In this work, mutations C150T, T489C, G3010A, C5178A, C8414T and A10398G have been reported as longevity-related. Then, after doing further analysis, I can conclude that most of them represent an advantage for the individual, although in a low level. It would be of interest to take into account all the longevity-related mutations to perceive a significant change.

References

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