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Comparison of telomere length between population-specific mitochondrial haplogroups among different age groups in a Latvian population

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ABSTRACT

Population studies have demonstrated that telomere length (TL) displays great diversity among different populations. Previously described controversial findings associated longevity with specific mitochondrial DNA haplogroups (hgs) (e.g., *J* and *U*). These observations may be influenced by population diversity, geographic location, and/or specific historic background. The aims of this study were to identify a specific hg which correlates with aging in a Latvian populating and to evaluate the possible association of TL variability with specific mitochondrial hgs. The results show no significant correlation between TL, mitochondrial DNA hgs and longevity. A slight increase in frequency was observed among centenarians of hg *H*; however, these findings were not statistically significant. TL did not show any statically significant difference, only hg *W* had slightly longer telomeres among others. An insignificant increase in TL was observed in the 55–89 age group of hg *W* but in the <90 age group for hg *J* which also had the longest TL in the 20–45 age group. In conclusion this study indicates that specific mitochondrial DNA hgs do not have a significant, if any, influence on the variation of TL in Latvians.

1. Introduction

Mitochondrial DNA (mtDNA) is maternally inherited, and many inherited variants of mtDNA, i.g. hgs do exist, that are geographically distributed. Previous studies have shown that some of hgs are associated with common complex traits and a possible connection between age-related diseases, longevity, mitochondrial haplogroup background and population divergences (e.g., Tanaka et al., 1998; Czarnecka and Bartnik 2011). A human mitochondrial hg defines differences in human mtDNA by SNPs (single nucleotide polymorphisms) which lead to amino acid changes within the OXPHOS (oxidative phosphorylation) respiratory complexes. There are 9 major hgs found in Europe (H, I, J, M, T, U, V, W, and X) (Torroni et al., 1997; Kenney et al., 2014). Some researches suggest that human adoption to chronic cold and irregular caloric availability due to seasonal changes could influence evolution by disrupting mitochondrial hgs and also longevity (Wallace 2005; Robine et al., 2012). Resent findings support the hypothesis that different mtDNA hgs lineages from different geographic origins might take a part in diverse susceptibilities to age-related diseases. The large accumulation of SNPs can cause amino acid and functional changes, while others cause changes in the rates of replication and transcription of the mtDNA. Progressive loss of mitochondrial function in several tissues is a common feature of aging believed to be influenced by life-long production of reactive oxygen species (ROS) as by-products of oxidative metabolism leads to the accumulation of DNA and protein damages (Shigenaga et al., 1994; Bellizzi et al., 2006; Kenney et al., 2014).

Several conflicting studies have also evaluated the possible association of various hgs with healthy aging. Beckstead et al. indicates that hg *H* individuals may live longer when compared to hg *U* individuals, under calorie restriction (Beckstead et al., 2009). Numerous studies have observed that hg *J* is more abundant among centenarians, while hg *U* decreases among centenarians (de Benedictis et al., 1999; Rose et al., 2001). Conversely, Pinós et al. have refuted the observation that hg *J* is associated with longevity and have

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suggested that longevity is population-specific (Pinós et al., 2012). On the other hand several other studies have failed to find an association of longevity with hgs *H* and *U* (de Benedictis et al., 1999; de Benedictis et al., 2000; Pinós et al., 2012). A study by Benn et al. also concludes that there are no hg associations with mortality and longevity (Benn et al., 2008). It has also been shown, in a population from Finland, that hgs H and HV are less frequent among centenarians than hgs *U*, *J* and *U*8 (Niemi et al., 2003). Beside that, defined mutations in the genes of mtDNA associated with hgs *D*, *D*1, *H*1 have been described and are more frequently found among centenarians. These haplogroup-defining mutations may affect ATP (adenosine triphosphate) synthesis, suggesting that specific mitochondrial variants are associated with biochemical differences (Tanaka et al., 1998; Tanaka et al., 2000). Numerous studies have described specific hgs as being associated with healthy aging and having a protective or opposite effect on the occurrence of some diseases and tumors (e.g., Czarnecka and Bartnik, 2011). In particular, different hgs were associated with Leber's hereditary optic neuropathy, ichemic stroke, coronary artery disease and diabetic retinopathy and osteoarthritis (OA) (Torroni et al., 1997; Hudson et al., 2007; Kofler et al., 2009; Rego-Pérez et al., 2008). Other studies have found an effect of some hgs against ischemic stroke, Alzheimer disease and Parkinson's disease (Carrieri et al., 2001; van der Walt et al., 2003; Ghezzi et al., 2005; Gaweda-Walerych et al., 2008; Rosa et al., 2008).

Telomere shortening is thought to be a major theory of aging. Telomeres are specialized chromosomal DNA–protein structures that cap and protect the terminal regions of eukaryotic chromosomes. Telomeres are dynamic structures that become shorter with every division of a cell. Once a critical length is no longer maintained, the cell is not able to divide; this halt in cell division is thought to be a consequence of aging (Blackburn 2001). However, to date, only few studies have addressed the possible association of mitochondrial hgs with TL. Fernández-Moreno et al. examined TL in hg *J* individuals and showed that they have significantly longer telomeres than non-J carriers (Fernández-Moreno et al., 2011). Considering that both cell elements are involved in the process of aging and longevity, there could be a possible association between mitochondrial inherited polymorphisms and the dynamics of TL. The aim of this study was to identify correlations between distribution frequencies among different age groups of the most prevalent mitochondrial variants (hgs *H*, *U*, *T*, *J*, *V* and *W*) in a Latvian population and to investigate possible associations of these hgs with TL.

2. Materials and methods

2.1. Samples

Blood samples were collected from healthy individuals, without any disorders that are known to affect TL, in a Latvian population from age 20 to over 90 years old. In total, 772 individuals were enrolled in this study. All participants provided appropriate written informed consent for the use of their phenotypic and genetic data that were voluntarily provided via detailed health and heredity questionnaires. All samples were obtained from genome database of the Latvian population (VIGDB, bmc.biomed.lu.lv/lv/par-mums/saistitas-organizacijas/vigdb/). Samples from participants in the mitochondrial hg studies were divided into three age groups: 20–45 years old (control group, $n = 374$), 55–89 years old (middle group, $n = 271$), and over 90 years old (centenarians, $n = 127$). As only small part of the samples of DNA was obtained with enough high concentration and quality for TRF (terminal restriction fragments) assay, the TL was measured and hgs *H*, *U*, *T*, *J*, *V* and *W* were detected in 221 samples. Samples were selected with similar percentage frequency of hgs among age groups as in the whole sample cohort (Table 1). These samples were divided into the same age groups: 20–45 years old (control group, $n = 61$), 55–89 years old ($n = 80$) and over 90 years old (centenarians, $n = 80$). A 45–55 year old group was not included because this study focuses on elderly individuals, ages 60 and above. This elderly population has the highest mortality rate among Latvians.

2.2. Extraction of genomic DNA

Genomic DNA was extracted from the peripheral white blood cells (WBC) using the standard phenol–chloroform method as previously described (Sambrook et al., 1989).

2.3. Southern blots of terminal restriction fragments (TRFs)

The method described in Kimura et al. (2010) was used, with some modifications, to determine TL. Briefly, a Southern blot of TRFs was conducted using a Telo TAGGG telomere length assay kit (Roche, UK). Concentrated DNA (~1 μg) was digested with restriction endonucleases Hinf I (10 U) and Rsa I (10 U) (Kimura et al., 2010). Digested DNA samples, a DNA size marker (GeneRuler 1 Kb DNA ladder, Thermo Scientific, Lithuania), and the DIG molecular weight marker (Roche, UK) were loaded into a 0.8% agarose gel and run for 20 h (19 V and 25 mA) to resolve fragment sizes. The DNA in the gel was then depurinated in 0.25 M HCl for 10 min. Further, the gel with the samples was denatured in 0.5 L of 0.5 M NaOH and 1.5 M NaCl for two 20-min washes. The samples were neutralized in 1 L of 0.5 M tris-OH containing 3 M NaCl (pH 7.5) for two 20-min washes. The DNA was transferred to a positively charged nylon membrane (Amersham Hybond^{TM}-N^{+}, GE Healthcare Life Sciences, UK) for 2 h using a vacuum blotter (VacuGene Pump, Pharmacia Biotech, Sweden) with a 20× SSC transfer buffer solution that contained 0.3 M sodium citrate and 3 M NaCl (pH 7.0). DNA was fixed to a membrane using a 30-s UV exposure, and the membrane was briefly washed in 2× SSC solution. The subsequent steps were performed using the manufacturer's protocol for the Telo TAGGG telomere length assay kit (Roche, UK). The membrane was visualized on a high performance chemiluminescence film (GE Healthcare Life Sciences, UK). The film was scanned, and the TRF signal was detected. DNA migration distances were measured using the Kodak digital science D1 program (Kodak, US); the DIG ladder was used for molecular size reference. The optical density of the DNA fragments was measured using the ImageJ software (Rasband and ImageJ, 1997–2014). TL was calculated using the

Table 1
Comparison of the all haplogroups found in a Latvian population in the three age groups.

Age groups, years (No)	Haplogroups number (%)								
	H	*U*	*T*	*J*	*V*	*W*	*I*	HV	*X*
20–45 (374)	41.7 (156)	27.3 (102)	9.9 (37)	6.7 (25)	3.5 (13)	4.0 (15)	4.3 (16)	2.1 (8)	0.5 (2)
55–89 (271)	42.4 (115)	28.8 (78)	6.3 (17)	6.3 (17)	4.8 (13)	4.1 (11)	1.1 (3)	4.8 (13)	1.5 (4)
<90 (127)	48.8 (62)	21.3 (27)	10.2 (13)	4.7 (6)	6.3 (8)	3.9 (5)	1.6 (2)	2.3 (3)	0.8 (1)
Total	44.6 (333)	25.7 (207)	8.7 (67)	5.9 (48)	4.4 (22)	4.0 (31)	3.3 (21)	2.6 (24)	0.9 (7)

For hgs *H*, *U*, *T*, *J*, *V* and *W*. Hgs – mitochondrial haplogroups, TL– telomere length, df – degrees of freedom, F – fixation indices.

following equation: mean TRF length = Σ (ODi)/Σ (ODi/Li), where ODi = optical density at position i and Li = TRF length at position i.

2.4. Mitochondrial genotyping

To confirm the hg affiliation of mitochondrial sequences, hierarchical PCR–RFLP analysis was performed using 17 restriction endonucleases: *Ava*II, *Dde*I, *Bsh*1236I, *Hae*III, *Hha*I, *Hinf*I, *Mbo*I, *Rsa*I, *Nla*III, *Acc*I, *Bst*OI, *Mse*I, *Alw*44I, *Ssp*I, *Eco*47I, and *Bsu*RI (van Oven and Kayser, 2009) The classification of hgs was based on their position in the hierarchy of the mitochondrial phylogenetic tree (www.phylotree.org, van Oven and Kayser, 2009).

2.5. Statistical analysis

All statistical analyses were performed using the R 3.1.1 (Core Team, 2014) software program. The statistical significance of the differences between the observed distributions of mitochondrial hgs in three age groups was evaluated with the *G*-test. Analysis of variance (ANOVA) was used to test differences of mean TL values for age groups and mitochondrial hgs. In this analysis, only hgs *H*, *U* and *T* were included because they had replicates for each combination within each age group. A *P* value equal to or less than 0.05 was considered significant.

3. Results

3.1. Distribution of mitochondrial haplogroups among different age groups

Mitochondrial hgs were analyzed among 772 individuals of three age groups (age 20–45, 55–89, over 90 years) in a Latvian population (Table 1). Hg *H* represents 7.1% more of the population among centenarians than in the control group. Only those individuals bearing hg *V* showed a gradual growth with increasing age (1.3% more in the age group 55–89 when compared to the control group; 2% more in the group >90 age group when compared to the 55–89 group). Interestingly, hg *U*, despite being the second most abundant hg among centenarians, shows a 7.5% decrease compared to the 55–89 age group. Hg *T* is equally represented both in the control and centenarian groups but less in the middle group. Hg *I* shows an obvious decrease, averaging 2.9%, in both the 55–89 and >90 age groups. Other hgs do not demonstrate a noteworthy gradual decrease or increase in distribution frequencies among the analyzed age groups. A *G*-test ($G = 20.53$, df = 16 un $P = 0.1971$) emphasizes that none of the hgs investigated show a significant association with longevity.

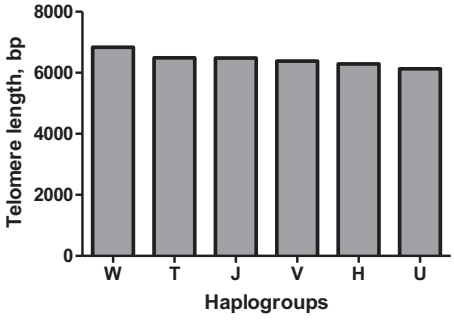

Fig. 1. Variation of telomere length for the hgs *H*, *U*, *T*, *J*, *V* and *W*. TRF-terminal restriction fragments, bp – base pairs.

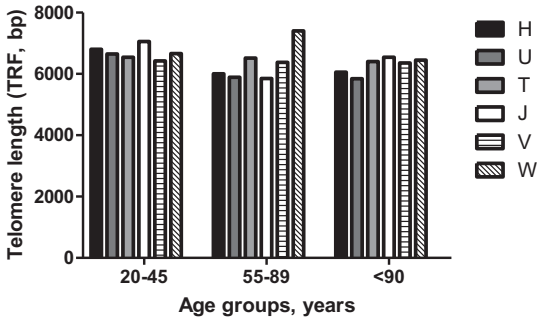

Fig. 2. Comparison of telomere length for the hgs *H*, *U*, *T*, *J*, *V* and *W* in three different age groups. 20–45, $n = 61$; 55–89, $n = 80$; <90 $n = 80$. TRF – terminal restriction fragments, bp-base pairs.

Table 2
Results of dispersion analysis (ANOVA).

TL	Hierarchical method				
	df	Sum of squares	Mean square	*F*	*P* value
Hgs	5	7840991	1568198	1.637	0.151748
Hgs: age	10	7888462	788846	0.823	0.606487
Residuals	203	194486331	958061	–	–

3.2. Association of telomere length with mitochondrial haplogroups and aging

A comparison of TL among different mitochondrial hgs in all together studied age groups is shown in Fig. 1. The average TL for hgs is: *H* (~6290 bp), *U* (~6130 bp), *T* (~6490 bp), *J* (~6480 bp), *V* (~6390 bp) and ~6840 bp). Consequently, there were a limited number of samples that were available for TL testing for hgs *I*, HV and *X*. There are no statically significant differences of average TL among hgs (ANOVA, $P = 0.1780$; $F = 1.542$; $R^2 = 0.03461$). Individuals belonging to hg *W* have the longest average TL, while those of hg *U* have the shortest average TL. Fig. 2 shows a comparison of the TL of individuals with hgs *H*, U, T, J, V and W in the three age groups separately. Hg *J* shows the longest TL in the control group and among centenarians. In the middle group hg *W* has the longest TL. Hgs *T* and *V* do not have obvious difference of TL among age groups. Results of the ANOVA analyses (Table 2) show that there are no significant correlations among TL, hgs and age in the Latvian population.

4. Discussion

Our previous study showed that the most common mitochondrial hgs in the Latvian population are *H* (44.5%), *U* (25.4%) and *T* (9.4%) (Pliss et al., 2006). In the current study none of hgs show statistically significant correlation with aging and the percentage varies slightly. The observed frequencies of hgs *H*, *U*, *T*, *J*, *V*, *I* and *X* were in stark contrast to those reported in a study from Finland (Niemi et al., 2003). Although Finland is geographically close to Latvia, hg *U* and cluster TJ were found to be more frequent than hg *H* among centenarians. The climate in Finland is only slightly colder than in Latvia and is considered to be similar. In one study, it was described that climate has an influence on human longevity (Robine et al., 2012). Although the climate is warmer, studies from South Europe showed a similar distribution of hg *J* to the Finnish population; however, the current study, along with other studies, did not support this finding (de Benedictis et al., 1999; de Benedictis et al., 2000; Pinós et al., 2012). Another study had similar observation regarding to hg *U* frequency in different age groups as it was in the current study (de Benedictis et al., 1999). One hypothesis describes a connection between population migration waves

to the North Europe and hg frequency that could be contributed to a necessary adaptation to the chronic cold and irregular caloric availability by varying mitochondrial metabolism (Wallace 2005). Hgs may play a protective role in colder climates by generating greater amounts of heat through higher electron transport rates and looser coupling or partially uncoupled OXPHOS. For the cold-adapted hgs, uncoupling mutations would produce less ATP per calorie consumption, which can be used for heat generation; therefore, more oxidized and less ROS would be formed (Mishmar et al., 2003; Baudouin et al., 2005; Wallace 2005). Mitochondrial hgs have different coupling efficiency (the percentage of oxygen consumption used for ATP synthesis rather than heat generation) and mitochondrial ROS production (Wallace, 2005). Previous observation suggests that hg *H* may not be as suitable as hg *U* for longevity in cold environments; however, this study contradicts this hypothesis. The Beckstead' research group showed that due to historic caloric restriction, longevity is observed in individuals with hg *H* compared to hg *U*, and that this longevity has not been changed during periods of caloric abundance (Beckstead et al., 2009). There are many parameters that can influence the survival of specific hgs in different environments. Differences of hgs frequencies during aging in various populations might be explained with diverse historical events and climate changes. As previously mentioned certain hgs have varying influences on diverse age-related diseases and tumors and therefore may slightly affect the frequency of specific hgs in older age groups.

Sahin et al. have proposed a theory connecting/linking telomere length with mitochondrial genetics. They have shown that short telomeres, which are sensed by cells as double-strand breaks and DNA instability, suppress PGC-1α/β (peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta) action via *p53* gene activation. These molecular interactions lead to mitochondrial dysfunction, cell senescence, growth arrest and apoptosis (Chin et al., 1999; Sahin and Depinho, 2010; Sahin et al., 2011; Rufini et al., 2013). PGC-1α/β regulates a vast amount of mitochondrion functions, including mitochondrial replication/transcription, OXPHOS, oxidative stress and gluconeogenesis, etc. (e.g., Wu et al., 1999; Lin et al., 2005). These mitochondrial outcomes, due to reduced electron transport chain efficiency due to chemical or genetic causes, lead to ROS production that cause a drop in ATP levels, leading to aging, which may limit lifespan as well as effect telomere length (Balaban et al., 2005; Moiseeva et al., 2009).

This study/current study demonstrates that the average TL in all mitochondrial hgs is similar and does not show statically significant differences among the hgs, however, some similarities with other studies can be observed. Martínez-Redondo et al. have shown that hg *H* has higher mitochondrial oxidative damage than hg *J*. In their study, hg *H* had higher oxygen uptake and therefore more ROS production than other hgs. The next highest level of oxygen uptake is found in hg *V* followed by hgs *T* and *U*, with the lowest level found in hg *J* (Martínez-Redondo et al., 2010). It has been shown that oxidative stress is associated with increased telomere attrition (von Zglinicki 2002; Kawanishi and Oikawa 2004). This means that TL should be shorter for hgs that produce more ROS, such as hg *H* compared to hg *U*. Similar interrelationship can be observed in our study for hg *H* (Fig. 1), however, it is not statistically significant. This hypothesis also might explain slightly longer telomeres for hg *J* among centenarians in the current/present study, due to less ROS accumulation during aging. Also previously, Fernández-Moreno et al. have shown that individuals with hg *J* have significantly longer telomeres than non-J carriers (Fernández-Moreno et al., 2011). However, Pinós et al. have found that hg *J* and longevity are not related and have proposed that different findings in previous reports could be due to a population-specific background (Pinós et al., 2012). Previously reported conflicting results related to TL may also be attributed to population-specific differences (Zole et al., 2013; Eisenberg et al., 2011; Salpea et al., 2008; Canela et al., 2007).

5. Highlights

Mitochondrial hgs are not significantly associated with longevity or longer telomere length in a Latvian population. Only hg *J* had slightly longer TL among centenarians. None of the hgs correlated with age either. Only hg *H* shows an insignificant increase of frequency among centenarians compared to the control group. Assuming that longevity and TL are either population-specific or geographically or historically specific, their association can be influenced by many factors during an individual's lifespan, environmental and genetic background.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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