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ORIGINAL INVESTIGATION

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Mitochondrial DNA polymorphisms associated with longevity in a Finnish population

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Abstract Sequence variation in mitochondrial DNA (mtDNA) may cause slight differences both in the functioning of the respiratory chain and in free radical production, and an association between certain mtDNA haplogroups and longevity has been suggested. In order to determine further the role of mtDNA in longevity, we studied the frequencies of mtDNA haplogroups and haplogroup clusters among elderly subjects and controls in a Finnish population. Samples were obtained from 225 persons aged 90–91 years (Vitality 90+) and from 400 middle-aged controls and 257 infants. MtDNA haplogroups were determined by restriction fragment length polymorphism. The haplogroup frequencies of the Vitality 90+ group differed from both those of the middle-aged controls (P=0.01) and the infants (P=0.00005), haplogroup H being less frequent than among the middle-aged subjects (P=0.001) and infants (P=0.00001), whereas haplogroups U and J were more frequent. Haplogroup clusters also differed between Vitality 90+ and both the middle-aged subjects (P=0.002) and infants (P=0.00001), the frequency of haplogroup cluster HV being lower in the former and that of UK and WIX being higher. These data suggest an association between certain mtDNA haplogroups or haplogroup clusters and longevity. Furthermore, our data appear to favour the presence of advantageous polymorphisms and support a role for mitochondria and mtDNA in the degenerative processes involved in ageing.

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Introduction

Longevity shows maternal inheritance, suggesting a role for mitochondrial DNA (mtDNA) in the process of ageing (Abbott et al. 1978; Brand et al. 1991; Sont and Vandenbroucke 1993; Korpelainen 1999). MtDNA is a maternally inherited 16,568-bp haploid genome that encodes 13 subunits of the respiratory chain complexes. Its mutation rate is 10 times faster than that of the nuclear genome and, consequently, the mean pairwise difference between populations is approximately 50 (Ingman et al. 2000). This high mutation rate is attributable partly to the lack of an effective DNA repair mechanism and partly to the constant exposure of mtDNA to oxygen free radicals. Mitochondrial oxidative phosphorylation (OXPHOS) is a major contributor to oxygen free radicals, further supporting the role of mitochondria and mitochondrial DNA in ageing (Wei et al. 1998; De Benedictis et al. 2000; Golden and Melov 2001).

Polymorphisms in mtDNA may cause subtle differences in the encoded proteins and, thus, subtle changes in OXPHOS activity and free radical production. This predisposes an individual or people sharing the same mtDNA genotype to an earlier onset of degenerative cellular processes, such as the accumulation of somatic mtDNA mutations and a decline in OXPHOS capacity. Alternatively, some of the polymorphisms could be beneficial. Common polymorphisms in mtDNA determine classes of related genotypes, haplogroups, that can be detected by

restriction fragment length polymorphism (RFLP) analysis. The frequencies of mtDNA haplogroups vary between ethnic groups (Torroni et al. 1996; Richards et al. 1998; Wallace et al. 1999), the European population being almost exclusively distributed among the nine haplogroups designated as H, I, J, K, T, U, V, W and X, whereas haplogroups A, B, C, D and E are specific to Asian populations and haplogroups L1, L2 and L3 to African populations (Wallace et al. 1999).

An association has been reported between certain mtDNA haplogroups and longevity. The frequency of haplogroup J is significantly higher among male centenarians in northern Italy (De Benedictis et al. 1999) and sequencing of the entire mtDNA of 11 Japanese centenarians has revealed polymorphisms 3010G→A, 5178C→A and 8414C→T to be more frequent than in controls (Tanaka et al. 1998). Furthermore, 9055G→A has been found to be more frequent among French (Ivanova et al. 1998) and Irish centenarians (Ross et al. 2001) than in controls.

Sequence variation in mtDNA shows high homogeneity in the Finnish population (Finnilä et al. 2001). A clear West Eurasian pattern of polymorphisms has been detected and the frequency of the haplogroups is similar to that among other Europeans, with the exception of haplogroup U, which is more frequent than elsewhere in Europe (Finnilä et al. 2000; Meinilä et al. 2001). Interestingly, however, significant geographical differences in mtDNA haplogroup frequencies have been detected, even within the Finnish population (Meinilä et al. 2001). The proposed role of mtDNA in longevity has been based on differences in haplogroup frequencies between centenarians and controls. However, as the frequencies of mtDNA haplogroups vary between ethnic groups, and even within the same group depending on the geographical origins of the individuals, both the subjects under study and their controls should be collected from the same geographical region in order to be able to compare haplogroup frequencies reliably. We therefore set out to study mtDNA haplogroup frequencies among persons who had reached the age of 90 years and among middle-aged controls ascertained from a defined geographical region in Finland.

Subjects and methods

Subjects

Samples were obtained from 225 persons aged 90 or 91 years (Vitality 90+) living in the city of Tampere, Finland; the group comprised 46 men (20.4%) and 179 women (79.6%), 161 of whom lived independently at home, and 63 were institutionalized. The Vitality 90+ group included unrelated subjects with the exception of one pair of twins and one pair of siblings. The control group (age range: 18–65 years; mean age: 40.5 years) consisted of 400 healthy blood donors, samples from whom were obtained anonymously from the Finnish Red Cross Office in Tampere. Anonymous samples were also obtained from 257 infants (age range: 2–12 months; mean: 6.5 months) born at Tampere University Hospital. Therefore, no information was available on the ancestry of the subjects in the two control groups, although the infants were born during a 10-month period suggesting that the probability of siblings among them was low. Information from hospital records of the Vitality 90+ subjects was used to evaluate the role of the mtDNA haplogroups as risk factors for diseases, such as coronary artery disease, heart failure, peripheral artery arteriosclerosis, stroke, heart infarction, pulmonary embolism, cancer, diabetes, dementia and Parkinson's disease.

Methods

Total DNA was isolated from blood by using a QIAamp Blood Kit (Qiagen, Hilden, Germany) or, in the case of the infants, by using a non-enzymatic salt precipitation method (Lahiri and Nurnberger 1991). MtDNA haplogroups were determined by restriction fragment analysis (Finnilä et al. 2001). The 3010G→A polymorphism defining the haplogroup subclusters H1 and J1 was analysed by conformation-sensitive gel electrophoresis, in which a fragment spanning nucleotides 2866 and 3263 was amplified and subjected to analysis as described earlier (Finnilä et al. 2000).

Differences in the frequencies of mtDNA haplogroups and haplogroup clusters between the populations were evaluated by using the exact test of population differentiation (Rousset and Raymond 1995) as implemented in ARLEQUIN 2.0 (Schneider et al. 2000) or, if applicable, by the $\chi 2$ test or Fisher's exact test.

Results

Frequencies of mtDNA haplogroups among Vitality 90+ cases and controls

MtDNA haplogroups were determined in 882 samples including 225 from the Vitality 90+ group, 400 from healthy controls and 257 from infants. All the samples except for six belonged to the ten mtDNA haplogroups that have been detected in the Finnish population (H, I, J, K, M, T, U, V, W and X). The haplogroup frequencies of the Vitality 90+ group differed from those of the controls (P=0.01; Table 1) in that the frequency of haplogroup H was lower (P=0.001), as was also the case with the closely related haplogroup V. No difference was found in the frequency of subcluster H1 between the Vitality 90+ group and the controls belonging to haplogroup H. On the other

Table 1 Haplogroup frequencies among the Vitality 90+ subjects, controls and infants

Haplogroup	Haplogroup frequencies					
	Vitality 90+		Controls		Infants	
	n	%	*n*	%	*n*	%
H	84	37.3	204	51.0	141	54.9
I	8	3.6	10	2.5	6	2.3
J	19	8.4	25	6.3	8	3.1
K	17	7.6	24	6.0	12	4.7
M	1	0.4	4	1.0	5	1.9
T	11	4.9	22	5.5	6	2.3
U	64	28.4	82	20.5	59	23.0
V	4	1.8	16	4.0	13	5.1
W	8	3.6	5	1.3	5	1.9
X	5	2.2	7	1.8	1	0.4
Other	4	1.8	1	0.3	1	0.4
Total	225	100.0	400	100.2	257	100.0

hand, the frequency of haplogroup U was higher (P=0.03) among the Vitality 90+ cases, as was the related haplogroup K. In order to substantiate the observed differences, we analysed a group of 257 infants and again found significant differences in haplogroup frequencies between Vitality 90+ and the infants (P=0.00005), but not between the controls and the infants (P=0.22).

Haplogroup J was present at a higher frequency among the Vitality 90+ subjects than in either the controls or the infants (Table 1) supporting previous findings among Italian centenarians (De Benedictis et al. 2000). Furthermore, the frequency of subcluster J1 was 4.0% in the Vitality 90+ group and 4.5% among the controls, whereas that of subcluster J2 was 4.4% in Vitality 90+ and 1.8% in the controls, suggesting that the higher frequency of haplogroup J in Vitality 90+ is attributable to an increase in subcluster J2.

Frequencies of mtDNA haplogroup clusters among Vitality 90+ cases and controls

We then analysed the frequencies of the clusters of phylogenetically related haplogroups HV, UK, TJ and WIX. Again, the Vitality 90+ group and the controls differed (P=0.002; Table 2), the frequency of cluster HV being lower among the Vitality 90+ cases (P=0.001), whereas that of cluster UK was higher (P=0.014). The number of samples belonging to cluster WIX was almost twice as high in the Vitality 90+ group as in the controls (P= 0.078).

The Vitality 90+ cases also differed from the infants in this respect (P=0.00001), their frequency of cluster HV being significantly lower (P=0.001), whereas those of clusters WIX (P=0.048) and UK (P=0.05) were higher and that of cluster TJ significantly higher (P=0.004). The controls and the infants did not differ significantly from each other (Table 2).

Association between mtDNA haplogroups and clinical phenotypes

The genotype-phenotype association was studied in the Vitality 90+ group after stratification according to the presence or absence of various clinical phenotypes. No differences were found in the frequency of mtDNA haplogroups among the affected and non-affected subjects, except with respect to diabetes mellitus (P=0.044), where the frequency of cluster UK was twice as high in patients as in those who were unaffected. Indeed, 15 out of the 25 patients with diabetes mellitus (60%) belonged to cluster UK, whereas only 32% of the non-diabetic subjects did so; furthermore, seven of the diabetics (28%) belonged to haplogroup K, the frequency of which was only 5% among the subjects without diabetes.

Table 2 Frequencies of mtDNA haplogroup clusters among the Vitality 90+ subjects, controls and infants

Cluster	Cluster frequencies					
	Vitality 90+		Controls		Infants	
	n	%	*n*	%	*n*	%
HV	88	39.1	220	55.0	154	59.9
WIX	21	9.3	22	5.5	12	4.7
TJ	30	13.3	47	11.8	14	5.4
UK	81	36.0	106	26.5	71	27.6
Other	5	2.2	5	1.3	6	2.3
Total	225	99.9	400	100.1	257	99.9

Discussion

We found significant differences in mtDNA haplogroup frequencies between the Vitality 90+ subjects and the controls. Haplogroup H was less frequent among the Vitality 90+ cases than among the middle-aged controls or the infants, whereas haplogroups J, U and K were more frequent. The differences in haplogroup frequencies between the three age groups were similar to the age-related trend in haplogroup frequencies detected in a series of approximately 800 Italians (De Benedictis et al. 2000). Furthermore, we found that the frequencies of related haplogroups had similar tendencies to increase or decrease in most cases and, in consequence, the haplogroup cluster HV was significantly lower among the Vitality 90+ subjects than among the controls, whereas those of clusters UK and TJ were higher. These data suggest an association between certain mtDNA haplogroups or haplogroup clusters and longevity.

The maternal lineage of the Vitality 90+ group and the two anonymous control groups was not known introducing a possible confounding effect. However, the Finnish population is ethnically homogeneous and immigration from other countries has been negligible (Korkiasaari and Söderling 1994). Migration within Finland remained at approximately 4% in the 20th century, increasing only to 5.5% between 1946–1950 (Koskinen et al. 1994). The settlement of Finns from southeastern Karelia after World War II has probably not affected the mtDNA gene pool, as there is no difference in haplogroup frequencies between the present Karelians and Finns (Simoni et al. 2000). Homogeneity among the three groups is further suggested by the observations that an mtDNA lineage introduced by earlier founders will make a larger contribution to the contemporary population than lineages introduced later (Heyer 1995). Therefore, we believe that the differences detected between Vitality 90+ and the two control groups represent true differences.

Like our finding that the frequency of haplogroup J increases with the age of the population, an association between this European-specific mtDNA haplogroup and longevity has also been reported among Italian centenarians (De Benedictis et al. 1999). Interestingly, we have found that the frequency of subcluster J2 is higher among the Vitality 90+ subjects than among the controls. Differences in the frequencies of haplogroup J subclusters have

also been reported in Irish centenarians and controls (Ross et al. 2001) but, unfortunately, the assignment to subclusters was based on the nucleotide sequence in HVS-I, thus not allowing comparison with the present data. Sequencing of HVS-I in Italian centenarians and controls has not revealed any clustering into a specific haplotype within haplogroup J (Rose et al. 2001). It has been suggested, however, that this haplogroup modulates the phenotypic expression of the mtDNA mutations 11778G→A and 14484T→C that cause Leber's hereditary optic neuropathy (LHON; Brown et al. 1997; Lamminen et al. 1997; Torroni et al. 1997), and the frequency of subcluster J1 has been found to be 8-fold among patients with LHON relative to controls (Torroni et al. 1997), suggesting that this subcluster increases the deleterious effect of an mtDNA mutation. Our data do not contradict this finding, as they suggest that subcluster J2 is beneficial in ageing. The nucleotide substitution 9055G→A defining haplogroup K is higher among French centenarians than among the controls (Ivanova et al. 1998) and we have found that this haplogroup is more frequent in the Vitality 90+ group (7.6%) than in either the controls (6.0%) or the infants (4.7%). Furthermore, the only clinical association among the Vitality 90+ subjects is between diabetes mellitus and haplogroup K.

The 5178C→A polymorphism has been shown to be more frequent among Japanese centenarians than among controls (Tanaka et al. 1998). Furthermore, the 5178C allele is more frequent among elderly hospital patients than among young ones suggesting that this allele predisposes subjects to late-onset diseases or that subjects having the 5178A allele remain healthier and live longer (Tanaka et al. 1998). The 5178C→A polymorphism defines haplogroup D, which is one of the four major Asian haplogroups (Torroni et al. 1993). Recent data on complete mtDNA sequences indicate that the 3010G→A polymorphism is the only sequence variant that is common to haplogroups D and J (Herrnstadt et al. 2002). However, this does not explain the associations detected among Japanese and European centenarians, as 3010G→A appears to have the opposite effects in these two populations. It is therefore obvious that sequence variation in the entire genome must be considered in order to account for the effects of mtDNA haplogroups on longevity.

Nucleotide changes in mtDNA, either non-synonymous substitutions in structural genes or substitutions in the biogenesis genes, form a continuum from deleterious mutations that cause early onset diseases to mildly deleterious polymorphisms that may predispose subjects to age-related degenerative diseases, to neutral variants, or even to polymorphisms that may be advantageous. The non-neutral evolution of mtDNA has been suggested by many authors (Watt and Dean 2000; Gerber et al. 2001) and an increased non-synonymous versus synonymous substitution rate has been taken to suggest the presence of mildly deleterious variants (Rand and Kann 1998; Watt and Dean 2000), although originally it was thought to result from adaptive fixation of advantageous mutations (McDonald and Kreitman 1991). The association between longevity and mtDNA haplogroups D and J suggest either advantageous polymorphisms within these haplogroups or mildly deleterious polymorphisms within the remaining haplogroups. In order to test the hypothesis that new polymorphisms are part of an adaptive evolution, we calculated the average substitution frequencies for the mtDNA haplogroups by using data on 192 complete mtDNA sequences from Finns (Finnilä et al. 2001). A haplotype lying between the African, Asian and European haplogroups was taken to be the most recent common ancestor. Surprisingly, the average frequency of substitutions was higher in those haplogroups that were found more frequently among the Vitality 90+ subjects (Fig. 1). The data therefore suggest that some substitutions can be advantageous, supporting the hypothesis of adaptive evolution.

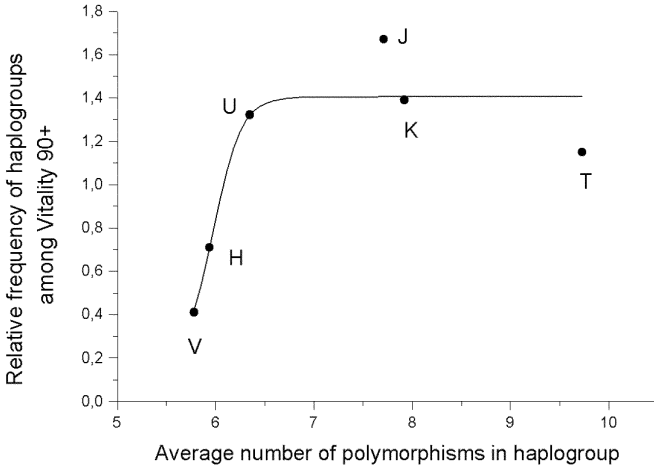

Fig. 1 Relative frequencies of mtDNA haplogroups among the Vitality 90+ subjects, plotted against the average numbers of polymorphisms in haplogroups. The average numbers of non-synonymous substitutions in the structural genes and substitutions in genes encoding ribosomal RNAs and tRNAs were calculated for each haplogroup, by making use of 192 Finnish mtDNA sequences (Finnilä et al. 2001). The haplotype lying between the African, Asian and European haplogroups was taken to be the most recent common ancestor. A sigmoidal fit to the data points is shown (χ^2 test, P=0.068). The *capital letters* refer to mtDNA haplogroups. Haplogroups I, W and X were not included in the analysis, because their frequencies were below 4% in both of the control groups

We have found an association between certain mtDNA haplogroups or haplogroup clusters and longevity. Each of the mtDNA haplogroups is determined by a single ancient polymorphism, even though they harbour a great number of other nucleotide variants. Polymorphisms in mtDNA may be mildly deleterious, causing a subtle decrease in OXPHOS activity and an increase in the frequency of somatic mtDNA mutations. The differences in mtDNA haplogroup frequencies between the present Vitality 90+ group and the controls suggest either a contribution from mildly deleterious polymorphisms that shorten the life span in the younger age groups or from advantageous polymorphisms that lengthen the life span in the elderly. Our data appear to favour the presence of advantageous polymorphisms and support a role for mi-

tochondria and mtDNA in the degenerative processes involved in ageing.

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