AGE (2012) 34:227–233
DOI 10.1007/s11357-011-9209-5

Are mitochondrial haplogroups associated with extreme longevity? A study on a Spanish cohort

Tomàs Pinós · Gisela Nogales-Gadea · Jonatan R. Ruiz · Gabriel Rodríguez-Romo · Catalina Santiago-Dorrego · Carmen Fiuza-Luces · Félix Gómez-Gallego · Amalia Cano-Nieto · Nuria Garatachea · María Morán · Miguel Angel Martín · Joaquín Arenas · Antoni L. Andreu · Alejandro Lucia

Received: 21 October 2010 / Accepted: 11 January 2011 / Published online: 28 January 2011

Abstract Mitochondrial haplogroups could influence individual susceptibility to mitochondrial DNA (mtDNA) damage, and human longevity, as indicated by previous studies with Caucasian (European) or Asian cohorts. Here, we compared the frequency of mtDNA haplogroups in a group of Spanish (Caucasian) centenarians (n=65, aged 100–108 years, 58 women, most from the central part of Spain) and a group of healthy young adults (n=138, 62 women, aged 20–40 years) of the same ethnic origin. We did not find significant differences between centenarians and the control group (P>0.2). Only two centenarians (both women) had the haplogroup J, which hampered comparison with the control group (n=15, five women). Our data confirm that the potential effects of mitochondrial haplogroups on human longevity might be population/geographic

Tomàs Pinós, Gisela Nogales-Gadea, Antoni L. Andreu, and Alejandro Lucia are equal contributors.

T. Pinós · G. Nogales-Gadea · A. L. Andreu
Departament de Patología Mitocondrial i Neuromuscular, Institut de Recerca Hospital Universitari Vall d'Hebron, Barcelona, Spain

J. R. Ruiz
Unit for Preventive Nutrition, Department of Biosciences and Nutrition at NOVUM, Karolinska Institutet, Stockholm, Sweden

J. R. Ruiz
Department of Physical Activity and Sport, School of Physical Activity and Sport Sciences, University of Granada, Granada, Spain

G. Rodríguez-Romo
INEF, Universidad Politécnica, Madrid, Spain

C. Santiago-Dorrego · C. Fiuza-Luces · F. Gómez-Gallego · A. Lucia
Universidad Europea de Madrid, Madrid, Spain

A. Cano-Nieto
SUAP Archena, Hospital Morales Meseguer, Murcia, Spain

N. Garatachea
Faculty of Health and Sport Science, University of Zaragoza, Huesca, Spain

M. Morán · M. Angel Martín · J. Arenas
Laboratorio de enfermedades mitocondriales y neuromusculares, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain

T. Pinós · G. Nogales-Gadea · M. Morán · M. Angel Martín · J. Arenas · A. L. Andreu (✉)
CIBERER, Valencia, Spain
e-mail: aandreu@ir.vhebron.net

specific, with important differences between studies (notably, with regard to the previously reported potential benefit brought about by the haplogroup J) arising from the different living environment and ethnic background of the study cohorts.

Keywords Genetics · Mitochondria · Centenarians

Introduction

Mitochondria are one of the most important organelles for understanding the aging process (Vina et al. 2009). These organelles are both the main source and target of reactive oxygen species (ROS). Their DNA (mtDNA) is more exposed to oxidative damage than nuclear DNA owing to a lack of histone-mediated protection. Accumulation of mtDNA somatic mutations over the lifespan is one of the main features that accompany the age-related loss of mitochondrial function (Wallace et al. 2003). Because mtDNA *haplotypes* or *haplogroups* (i.e., nonpathogenic mtDNA populations that form a series of population-specific lineages) might influence individual susceptibility to mtDNA damage, they could also influence human longevity (De Benedictis et al. 1999; Ivanova et al. 1998; Niemi et al. 2003; Rose et al. 2002; Ross et al. 2001; Santoro et al. 2006; Tanaka et al. 1998; Yao et al. 2002).

The Caucasian haplogroup J is characterized by the mutations T489C, A10398G, A12612G, G13708A plus the T4216C, A11251G, and C15452A substitutions shared with haplogroup T and seems to confer a higher chance to attain high longevity than other mtDNA haplogroups in Northern Italians (De Benedictis et al. 1999), Northern Irish (Ross et al. 2001), Finns (Niemi et al. 2003), and Northern Spaniards (Dominguez-Garrido et al. 2009). The association between the haplogroup J and increased longevity was, however, not corroborated in Southern Italians (Dato et al. 2004) or in a Tunisian population (Costa et al. 2009). In the Japanese population, the D haplogroup (and specifically, the D4a haplogroup) is associated with longevity (Bilal et al. 2008; Tanaka et al. 1998); yet, this finding was not confirmed in Southern Chinese (Yao et al. 2002). Besides between-studies differences in the ethnic/geographic origin of the subjects, differences in the age of the "longevity" cohorts are also a potential confounder: while some reports studied centenarians, i.e., ≥100 years (Bilal et al. 2008; Costa et al. 2009; De Benedictis et al. 1999; Ivanova et al. 1998; Rose et al. 2001; Tanaka et al. 1998), others studies investigated younger people, e.g. ≤75 years (Yao et al. 2002), 85+ years (Dominguez-Garrido et al. 2009), 80–97 years (Ross et al. 2001), or 90–91 years (Niemi et al. 2003). One of the most suitable approaches for identifying candidate gene variants associated with "longevity assurance" is to study the genotype of centenarians (Martin et al. 2007). These people are the survival tail of the population since they escaped diseases of the pre-antibiotic era and have avoided or postponed age-related diseases and their fatal consequences (Salvioli et al. 2008).

It was the purpose of our study to compare the frequency distribution of mtDNA haplogroups among a group of Spanish (Caucasian) centenarians and a cohort of healthy young adults (aged <40 years) of the same ethnic origin.

Material and methods

The study was approved by the ethics committee of the *Universidad Europea de Madrid* (Spain). A written informed consent was obtained from each participant. The study conformed to the standards set by the latest revision of the Declaration of Helsinki. Our study was designed and performed in accordance with the recommendations for the human genotype–phenotype association studies recently published by the *NCI-NHGRI Working Group on Replication in Association Studies* (Chanock et al. 2007). These recommendations include among others, the following items: indicating time period and location of subject recruitment, success rate for DNA acquisition, or sample tracking methods.

Participants

Participants were of the same Caucasian (Spanish) descent for ≥3 generations. The majority (~85%) of them were born and lived in the same areas of Spain (*Castilla-León*, *Castilla La Mancha, Comunidad de Madrid*).

Young adults (controls, n= 138)

We used a group of blood donors of both sexes from the "Hospital 12 de Octubre" of Madrid (Spain) who were used as the control population in a recent study in the field (Dominguez-Garrido et al. 2009); they

showed no significant difference with the Spanish haplogroup distribution previously reported (Ruiz-Pesini et al. 2000). All subjects of this group were (1) aged 20–40 years, (2) non-alcoholic or drug consumer, and (3) had no cardiovascular disease.

Centenarians (cases, n=65)

During 2009–2010, we obtained DNA from saliva samples in centenarians (n=42) of both sexes living in the Madrid area, in several nursing residencies (n=32), or at home (n=10). In spring 2010, we also gathered saliva samples of 13 centenarians living in five nurse residencies of *León* (located ~350 km away from Madrid, in Spain), or Murcia (n=10, ~400 km away from Madrid). The age range of the centenarians was 100–108 years. The most prevalent diseases in the total centenarians' cohort (n=65) were osteoarthritis (72%), hypertension (63%), dementia (49%), and coronary artery disease (29%). Three centenarians were free of any diagnosed disease.

Genotyping

Genotype analysis of the control group has been described elsewhere (Dominguez-Garrido et al. 2009). Genotyping of centenarians was performed in the Hospital *Vall d'Hebron* (Barcelona, Spain) using a similar methodology, i.e., PCR amplification of short mtDNA fragments followed by restriction enzyme analysis (RFLP) or by sequencing in the cases of haplogroups HV and K. To ensure proper internal control, for each genotype analysis, we used positive and negative controls from different mtDNA aliquots which were previously genotyped by the same method according to recent recommendations for replicating genotype–phenotype association studies (Chanock et al. 2007). For all polymorphisms, the resulting RFLP analysis was scored by two experienced and independent investigators who were blind to subject data.

Information on the primers, PCR annealing temperature, restriction enzymes, and fragments obtained for each polymorphism, respectively, for all studied polymorphisms is shown in Table 1.

Statistical analysis

All statistical analyses were performed using the PASW (v. 18.0 for WINDOWS, Chicago). Mitochondrial haplogroup frequencies were compared among Spanish young adults (*controls*) and centenarians (*cases*) using a χ^2 test with α set at 0.05.

Results

Table 2 shows the haplogroup frequencies for both centenarians and controls. Since the control group did not have the K, HV*, W, X, and L haplogroups, we grouped them into the category O. We did not find significant differences between centenarians and the control group (P>0.2). Only two centenarians (both women) had the haplogroup J, which hampers comparisons with the control group (n=15, five women). We further examined whether the H group (versus non H) was associated with longevity using logistic regression analysis after adjusting for age and sex; yet, we did not observe a significant association (P>0.2).

Discussion

The main finding of our study was that mtDNA haplogroups are not associated with longevity, at least in Spanish (Caucasian) centenarians from the main, central area of the country. As such, our findings do not corroborate those of previous research showing that the Caucasian haplogroup J confers a higher chance to attain high longevity in northern Italians (De Benedictis et al. 1999), Northern Irish (Ross et al. 2001), Finns (Niemi et al. 2003), and Northern Spaniards (Dominguez-Garrido et al. 2009). Our data are in agreement with those of Dato and coworkers, reporting no association between the aforementioned haplogroup and increased longevity in Southern Italians (Dato et al. 2004), and also with recent findings on the Tunisian population (Costa et al. 2009). The present confirm and strengthen the original hypothesis by Dato and coworkers (who did not specifically study a centenarians' cohort as we did here): when existing, the possible effect of mitochondrial haplogroups on longevity seems to be population specific (Dato et al. 2004).

Rate of aging and survival are partly heritable traits, with some genetic variants contributing to exceptional lifespan; centenarians are theoretically enriched with such variants some of which could be located in the mitochondrial genome (Salvioli et al. 2008). Indeed, the mutation rate of mtDNA over the years is very high

Table 1 Genotyping methods for each polymorphism

Polymorphism	Haplogroup	Restriction enzyme	RFLP	Primers
C7028T	H	*AluI*	C: 278, 219, 188, 139, 61 bp	5′-CTCTTCGTCTGATCCGTCCT-3′
			T: 278, 219, 158, 139, 61, 30 bp	5′-AGCGAAGGCTTCTCAAATCA-3′
G4580A	V	*NlaIII*	G: 377, 361, 99, 66 bp	5′-TGGCTCCTTTAACCTCTCCA-3′
			A: 460, 377, 66 bp	5′-AAGGATTATGGATGCGGTTG-3′
T14766C	HV	–		5′-GCATAATTAAACTTTACTTC-3′
				5′-AGAATATTGAGGCGCCATTG-3′
A12308G	UK	*HinfI*	A: 168, 67 bp	5′-CTCAACCCCGACATCATTACC-3′
			G: 138,67, 30 bp	5′-ATTACTTTTATTTGGAGTTGCACCAA**G**ATT-3′
T14798C	K	-		5′-GCATAATTAAACTTTACTTC-3′
				5′-AGAATATTGAGGCGCCATTG-3′
T4216C	JT	*NspI*	T: 903 bp	5′-TGGCTCCTTTAACCTCTCCA-3′
			C: 460, 443 bp	5′-AAGGATTATGGATGCGGTTG-3′
G13704A	J	*BstNI*	G: 582, 387 bp	5′-ACATCTGTACCCACGCCTTC-3′
			A: 969 bp	5′-AGAGGGGTCAGGGTTCATTC-3′
A4917G	T	*BfaI*	A: 345, 223, 204, 101, 90, 15 bp	5′-ACTAATTAATCCCCTGGCCC-3′
			G: 306, 223, 204, 101, 90, 39, 15 bp	5′-CCTGGGGTGGGTTTTGTATG-3′
G8894A	W	*HaeIII*	G: 241, 238, 156, 69, 48, 31, 28, 4 bp	5′-TTTCCCCCTCTATTGATCCC-3′
			A: 241, 238, 187, 69, 48, 28, 4 bp	5′-GTGGCCTTGGTATGTGCTTT-3′
T4470C	X	*AccI*	T: 937 bp	5′-TGGCTCCTTTAACCTCTCCA-3′
			C: 551, 386 bp	5′-AAGGATTATGGATGCGGTTG-3′

For all polymorphisms, the general cycle of PCR consisted of 5 min at 94°C, followed by 30 cycles of 30 s at 94°C, 45 s at 61°C and 1 min at 72°C; these cycles were followed by a final extension step of 7 min at 72°C. All restriction enzymes were obtained from New England Biolabs (Beverly, MA, USA). "–" indicates that the polymorphism was analyzed by sequencing. Restriction Fragment Length Polymorphism (RFLP) shows the band pattern obtained depending on the nucleotide. These DNA fragments were analyzed in agarose gels ranging between 0.8% and 2% agarose, depending on the molecular weight of the bands in the RFLP. One of the primers used in the analysis of the A12308G polymorphism includes a nucleotide mismatch highlighted in bold

compared with nuclear DNA owing to a much less-efficient repair system (Ballard and Dean 2001). Further, accumulation of mtDNA somatic mutations over life could also be a cause (rather than a consequence) of aging, particularly in post-mitotic neuronal cells (Bohr et al. 2007; Salvioli et al. 2008). Although in general, the mtDNA mutations that form mtDNA haplogroups are thought to be non-pathological per se, they might modulate mitochondrial metabolism (leading to mild differences in OXPHOS activity), and they could also affect the cross-talk that exists between nuclear and mitochondrial genomes (Ruiz-Pesini et al. 2000; Santoro et al. 2006). Research on mouse cell lines that were homogeneous for their nuclear genome but differed in their mtDNA showed that mtDNA haplogroups influence cell respiration and anti-ROS defenses (Moreno-Loshuertos et al. 2006). Thus, mtDNA mutations could have some significant phenotype effects, e.g., they could influence the risk of neurodegenerative diseases (van der Walt et al. 2003, 2004) as well as modulate the biochemical defects and clinical outcome of these disorders (D'Aurelio et al. 2010), affect spermatozoa motility (Montiel-Sosa et al. 2006; Ruiz-Pesini et al. 2000), or influence the development of mitochondrial disorders (Gil Borlado et al. 2010). They could also have an effect in human longevity, at least in some ethnic/geographical cohorts (De Benedictis et al. 1999; Ivanova et al. 1998; Niemi et al. 2003; Rose et al. 2002; Ross et al. 2001; Santoro et al. 2006; Tanaka et al. 1998; Yao et al. 2002).

Dominguez-Garrido and coworkers recently reported that the Caucasian haplogroup J (which was associated with lower mtDNA damage) seems to confer a higher chance to attain high longevity (85+ years) compared with other mtDNA haplogroups in Northern Spaniards (Dominguez-Garrido et al. 2009). Such association could not be corroborated in the present study of centenarians coming mainly from the central part of Spain. Comparisons between the present data and those by Dominguez-Garrido et al.

Table 2 Haplogroup frequencies for both centenarians and controls

	Centenarians						Control					
	All (n=65)		Female (n=58)		Male (n=7)		All (n=138)		Female (n=62)		Male (n=76)	
H	37	(56.9)	31	(53.4)	6	(85.7)	61	(44.2)	30	(48.4)	31	(40.8)
J	2	(3.1)	2	(3.4)			15	(10.9)	5	(8.1)	10	(13.2)
T	6	(9.2)	6	(10.3)			8	(5.8)	4	(6.5)	4	(5.3)
U	9	(13.8)	9	(15.5)			32	(23.2)	14	(22.6)	18	(23.7)
K	1	(1.5)	1	(1.7)								
HV*	1	(1.5)	1	(1.7)								
V	3	(4.6)	2	(3.4)	1	(14.3)	8	(5.8)	2	(3.2)	6	(7.9)
W	2	(3.1)	2	(3.4)								
X	2	(3.1)	2	(3.4)								
L	1	(1.5)	1	(1.7)								
O	1	(1.5)	1	(1.7)			14	(10.2)	7	(11.3)	7	(9.2)

Values are frequencies (%)

(2009) are difficult owing to the fact that, although we used the same control group, in our study, all cases were centenarians, whereas in their study, 64% of cases were aged 85–90 years and the total number of centenarians was not reported. In their study, the J mitochondrial haplogroup was overrepresented in elderly from two areas of the North of Spain, i.e. a mountain area (Pyrenees, 26.1%) and a valley area (Ebro, 15.9%). None of our centenarians was born in the aforementioned areas and the frequency of the J haplogroup in our centenarians' cohort was of only 3.1% (n=2) vs. 10.9% (n=15) in the control group. Specifically, in elderly from the Pyrenees, the J2 haplogroup (defined by the G15257A mutation in the cytochrome b, leading to lower levels of mitochondrial ATP production), together with altitude (and thus mild hypoxia) exposure would theoretically lead to lesser ROS production and thus lesser mtDNA damage, which could benefit survival at late life. The J haplogroup is also associated with low OXPHOS efficiency, leading to a waste of heat that could be of benefit in colder areas (e.g. Pyrenees), yet not in warmer, more southern areas of Spain such as those in which most of our centenarians were born and lived (Mishmar et al. 2003; Ruiz-Pesini et al. 2004).

It thus seems that the survival benefits (or disadvantages) of a given mitochondrial haplogroup depends on the ethnic background of the study cohort as well as on the living environment. Several environmental factors (e.g. dietary habits including antioxidant intake, physical activity levels, work, and daily life stress) that can affect health status and thus survival potential, can vary considerably among ethnic groups, and could even mask the potential association between mtDNA haplogroups and longevity in some cohorts such as the one we studied here. It could be also hypothesized that the potential influence of mitochondrial haplogroups on longevity might vary among different populations depending on the types of diseases that are more prevalent in each population (i.e., whether these diseases are or are not strongly associated with oxidative damage).

We believe the strength from our study comes from our group of cases, i.e., being all centenarians. Indeed, a well-accepted approach for identifying those genetic factors that are associated with 'longevity assurance' is to study the genotype of centenarians. These people are the survival tail of population, and living 100 or more years is a rare phenotype in most countries, i.e. ≤1 every 10,000 people (Martin et al. 2007; Salvioli et al. 2008). On the other hand, we realize our results should be taken with caution due to the relatively low number of centenarians we studied. Nevertheless, we believe that the low sample size can be justifiable given the uniqueness of this type of population and the difficulty of finding suitable controls for any centenarians' cohort. Further research is necessary using other more complete approaches aiming at determining if mtDNA haplogroups influence "resistance" to diseases and attenuation of functional decline as people age, e.g. longitudinal designs starting in the middle life of humans who are still disease-free at this point (Martin et al. 2007).

Longevity is likely a complex, polygenic trait, which could be influenced by numerous gene–environment and gene–gene interactions, including those interactions between genetic variants that might not influence longevity *individually*. For instance, it remains to be determined if the interaction of mtDNA haplotypes with genetic variants in the nuclear genome exerts a potential effect on longevity (particularly, with those nuclear genes that modulate mitochondrial biogenesis, i.e., genes of the peroxisome proliferator-activated receptor γ coactivator 1α–nuclear respiratory factor–mitochondrial transcription Factor A pathway).

In summary, mitochondrial haplogroups are not associated with longevity in centenarians from Spain (mainly from its main middle part). It seems that the potential influence of mitochondrial haplogroups on longevity is population-specific, that is, the genetic and environmental background of each population cohort strongly influence the potential effect that mtDNA mutations might have on longevity.

Acknowledgments This study was partially supported by grants from Science and Innovation Ministry of Spain, Instituto de Salud Carlos III (ISCIII), refs. # PS09/00194, PS 09/01359* and PI07/0347; M Moran is a recipient of a ISCIII-Sara Borrell post-doctoral fellowship number CD06/00031; Gisela Nogales-Gadea is a recipient of a ISCIII-Sara Borrell post-doctoral fellowship number CD10/00027; and Jonatan Ruiz is a recipient of a grant of the Spanish Ministry of Science and Innovation (RYC-2010-05957).

References

Ballard JW, Dean MD (2001) The mitochondrial genome: mutation, selection and recombination. Curr Opin Genet Dev 11:667–672

Bilal E, Rabadan R, Alexe G, Fuku N, Ueno H, Nishigaki Y, Fujita Y, Ito M, Arai Y, Hirose N, Ruckenstein A, Bhanot G, Tanaka M (2008) Mitochondrial DNA haplogroup D4a is a marker for extreme longevity in Japan. PLoS ONE 3: e2421

Bohr VA, Ottersen OP, Tonjum T (2007) Genome instability and DNA repair in brain, ageing and neurological disease. Neuroscience 145:1183–1186

Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr, Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS (2007) Replicating genotype–phenotype associations. Nature 447:655–660

Costa MD, Cherni L, Fernandes V, Freitas F, Ammar El Gaaied AB, Pereira L (2009) Data from complete mtDNA sequencing of Tunisian centenarians: testing haplogroup association and the "golden mean" to longevity. Mech Ageing Dev 130:222–226

Dato S, Passarino G, Rose G, Altomare K, Bellizzi D, Mari V, Feraco E, Franceschi C, De Benedictis G (2004) Association of the mitochondrial DNA haplogroup J with longevity is population specific. Eur J Hum Genet 12:1080–1082

D'Aurelio M, Vives-Bauza C, Davidson MM, Manfredi G (2010) Mitochondrial DNA background modifies the bioenergetics of NARP/MILS ATP6 mutant cells. Hum Mol Genet 19:374–386

De Benedictis G, Rose G, Carrieri G, De Luca M, Falcone E, Passarino G, Bonafe M, Monti D, Baggio G, Bertolini S, Mari D, Mattace R, Franceschi C (1999) Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. FASEB J 13:1532–1536

Dominguez-Garrido E, Martinez-Redondo D, Martin-Ruiz C, Gomez-Duran A, Ruiz-Pesini E, Madero P, Tamparillas M, Montoya J, von Zglinicki T, Diez-Sanchez C, Lopez-Perez MJ (2009) Association of mitochondrial haplogroup J and mtDNA oxidative damage in two different North Spain elderly populations. Biogerontology 10:435–442

Gil Borlado MC, Moreno Lastres D, Gonzalez Hoyuela M, Moran M, Blazquez A, Pello R, Marin Buera L, Gabaldon T, Garcia Penas JJ, Martin MA, Arenas J, Ugalde C (2010) Impact of the mitochondrial genetic background in complex III deficiency. PLoS One 5:e12801

Ivanova R, Lepage V, Charron D, Schachter F (1998) Mitochondrial genotype associated with French Caucasian centenarians. Gerontology 44:349

Martin GM, Bergman A, Barzilai N (2007) Genetic determinants of human health span and life span: progress and new opportunities. PLoS Genet 3:e125

Mishmar D, Ruiz-Pesini E, Golik P, Macaulay V, Clark AG, Hosseini S, Brandon M, Easley K, Chen E, Brown MD, Sukernik RI, Olckers A, Wallace DC (2003) Natural selection shaped regional mtDNA variation in humans. Proc Natl Acad Sci USA 100:171–176

Montiel-Sosa F, Ruiz-Pesini E, Enriquez JA, Marcuello A, Diez-Sanchez C, Montoya J, Wallace DC, Lopez-Perez MJ (2006) Differences of sperm motility in mitochondrial DNA haplogroup U sublineages. Gene 368:21–27

Moreno-Loshuertos R, Acin-Perez R, Fernandez-Silva P, Movilla N, Perez-Martos A, Rodriguez de Cordoba S, Gallardo ME, Enriquez JA (2006) Differences in reactive oxygen species production explain the phenotypes associated with common mouse mitochondrial DNA variants. Nat Genet 38:1261–1268

Niemi AK, Hervonen A, Hurme M, Karhunen PJ, Jylha M, Majamaa K (2003) Mitochondrial DNA polymorphisms associated with longevity in a Finnish population. Hum Genet 112:29–33

Rose G, Passarino G, Carrieri G, Altomare K, Greco V, Bertolini S, Bonafe M, Franceschi C, De Benedictis G (2001) Paradoxes in longevity: sequence analysis of

mtDNA haplogroup J in centenarians. Eur J Hum Genet 9:701–707

Rose G, Passarino G, Franceschi C, De Benedictis G (2002) The variability of the mitochondrial genome in human aging: a key for life and death? Int J Biochem Cell Biol 34:1449–1460

Ross OA, McCormack R, Curran MD, Duguid RA, Barnett YA, Rea IM, Middleton D (2001) Mitochondrial DNA polymorphism: its role in longevity of the Irish population. Exp Gerontol 36:1161–1178

Ruiz-Pesini E, Lapena AC, Diez-Sanchez C, Perez-Martos A, Montoya J, Alvarez E, Diaz M, Urries A, Montoro L, Lopez-Perez MJ, Enriquez JA (2000) Human mtDNA haplogroups associated with high or reduced spermatozoa motility. Am J Hum Genet 67:682–696

Ruiz-Pesini E, Mishmar D, Brandon M, Procaccio V, Wallace DC (2004) Effects of purifying and adaptive selection on regional variation in human mtDNA. Science 303:223–226

Salvioli S, Capri M, Santoro A, Raule N, Sevini F, Lukas S, Lanzarini C, Monti D, Passarino G, Rose G, De Benedictis G, Franceschi C (2008) The impact of mitochondrial DNA on human lifespan: a view from studies on centenarians. Biotechnol J 3:740–749

Santoro A, Salvioli S, Raule N, Capri M, Sevini F, Valensin S, Monti D, Bellizzi D, Passarino G, Rose G, De Benedictis G, Franceschi C (2006) Mitochondrial DNA involvement in human longevity. Biochim Biophys Acta 1757:1388–1399

Tanaka M, Gong JS, Zhang J, Yoneda M, Yagi K (1998) Mitochondrial genotype associated with longevity. Lancet 351:185–186

van der Walt JM, Nicodemus KK, Martin ER, Scott WK, Nance MA, Watts RL, Hubble JP, Haines JL, Koller WC, Lyons K, Pahwa R, Stern MB, Colcher A, Hiner BC, Jankovic J, Ondo WG, Allen FH Jr, Goetz CG, Small GW, Mastaglia F, Stajich JM, McLaurin AC, Middleton LT, Scott BL, Schmechel DE, Pericak-Vance MA, Vance JM (2003) Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. Am J Hum Genet 72:804–811

van der Walt JM, Dementieva YA, Martin ER, Scott WK, Nicodemus KK, Kroner CC, Welsh-Bohmer KA, Saunders AM, Roses AD, Small GW, Schmechel DE, Murali Doraiswamy P, Gilbert JR, Haines JL, Vance JM, Pericak-Vance MA (2004) Analysis of European mitochondrial haplogroups with Alzheimer disease risk. Neurosci Lett 365:28–32

Vina J, Gomez-Cabrera MC, Borras C, Froio T, Sanchis-Gomar F, Martinez-Bello VE, Pallardo FV (2009) Mitochondrial biogenesis in exercise and in ageing. Adv Drug Deliv Rev 61:1369–1374

Wallace DC, Ruiz-Pesini E, Mishmar D (2003) mtDNA variation, climatic adaptation, degenerative diseases, and longevity. Cold Spring Harb Symp Quant Biol 68:479–486

Yao YG, Kong QP, Zhang YP (2002) Mitochondrial DNA 5178A polymorphism and longevity. Hum Genet 111:462–463