Negative results

Frailty and mortality are not influenced by mitochondrial DNA haplotypes in the very old

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1. Introduction

Human longevity shows heritability of ~25%, but large-scale, nuclear, genome-wide association studies have not yet clearly established all the responsible genes (Beekman et al., 2013; Kirkwood et al., 2011). In addition to nuclear genes, there may also be contributions from the maternally inherited, extranuclear, mitochondrial genome (mitochondrial DNA [mtDNA]). mtDNA codes for 13 respiratory chain proteins that are essential for the production of adenosine triphosphate, which is required for all active intracellular processes. There is an emerging evidence that mitochondrial dysfunction plays a key role in cellular aging, and the accumulation of somatic mutations of mtDNA is associated with an aging phenotype in mice and humans (Schon et al., 2012). It is, therefore, of great interest that different polymorphic variants of mtDNA appear to be enriched in cohorts of healthy older individuals, raising the possibility that our mitochondrial genome may influence how we age and how long we live. However, although several studies support this hypothesis (Niemi et al., 2003, 2005; Yang et al., 2012), there are conflicting findings and a lack of consistency (Courtenay et al., 2012; De Benedictis et al., 1999; Feng et al., 2011; Finnila et al., 2000; Ivanova et al., 1998; Ross et al., 2001; Tanaka et al., 1998, 2000). Moreover, there have been no studies of mtDNA and healthy aging phenotypes.

In an attempt to resolve these issues, we carried out a comprehensive study of mtDNA haplogroups in the Newcastle 85+ study. Ten mtDNA haplogroup markers effectively tag the most common subgroups of mtDNA found in 95% of the local population. The Newcastle 85+ study provides a unique opportunity to study the effects of these haplogroups both on survival up to and beyond age 85 and on frailty, an “unhealthy aging” phenotype, in a representative population-based cohort of the very old.

2. Experimental procedures

2.1. Study cohort

The Newcastle 85+ study has been reported and includes a sociodemographically representative 1921 birth cohort recruited at age ~85 through general practice patient lists (n = 845) (Collerton et al., 2009). An assessment of frailty was performed at baseline using 2 robust and validated measures: the Rockwood frailty index (RFI) (Rockwood and Mitnitski, 2007) and the Fried frailty status (FFS) (Fried et al., 2009), as described (Collerton et al., 2012). RFI was available for 811 (96.0%) of the cohort and FFS for 552 (65.3%). The cohort has been followed for mortality from baseline assessment (June 2006 to Sept 2007) until April 30, 2012.

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Table 1

Comparison of haplogroup frequencies across cohorts, percent (n)

| Mitochondrial haplogroup | Newcastle 85+ study age 85.5 y (SD 0.4), n = 700 | Local older cohort age 68.9 y (SD 8.5), n = 93 | 1958 MRC birth cohort, n = 2889 | Local birth cohort neonates, n = 344 |
|--------------------------|-------------------------------------------------|-----------------------------------------------|----------------------------------|----------------------------------|
| H                        | 46.0 (322)                                        | 36.6 (34)                                     | 44.2 (1278)                      | 39.8 (137)                      |
| V                        | 3.6 (25)                                          | 3.2 (3)                                       | 3.0 (87)                         | 3.5 (12)                        |
| J                        | 11.0 (77)                                         | 8.6 (8)                                       | 11.6 (336)                       | 9.9 (34)                        |
| T                        | 10.3 (72)                                         | 3.2 (3)                                       | 10.0 (289)                       | 13.1 (45)                       |
| U                        | 15.4 (108)                                        | 15.1 (14)                                     | 12.9 (374)                       | 15.1 (52)                       |
| K                        | 7.3 (51)                                          | 7.5 (7)                                       | 9.3 (269)                        | 7.8 (27)                        |
| Other (W, X, I, M classified here) | 6.4 (45)                                        | 25.8 (24)                                     | 8.9 (256)                        | 10.8 (37)                       |

Key: SD, standard deviation; MRC, Medical Research Council.

2.2. Molecular genetic analysis

mtDNA haplogroups were determined using a stepwise algorithm (Torroni et al., 1996) by primer extension of multiplex polymerase chain reaction products with the detection of the allelespecific extension products by matrix-associated laser desorption/ionization time of flight (Sequenom MassARRAY, San Diego, CA, USA). DNA was available for 752 participants; 52 cases were excluded from the analysis because of either heteroplasmatic status (n = 5) or inability to detect haplogroup/low-quality DNA (n = 47), leaving 700 with valid mitochondrial haplogroup data.

2.3. Statistical analysis

The frequency of mtDNA haplogroups in the incident Newcastle 85+ cohort (n = 700) was compared with 3 ethnically matched population control data sets representing different ages using chi-squared analysis with pairwise comparisons of samples for each haplogroup: (1) a local birth cohort (n = 344, neonatal cord blood samples), North Cumbria Community Genetics Project (Elliott et al., 2008); (2) a national mid-age cohort, the 1958 Medical Research Council cohort (n = 2889, 52% male), which has previously been shown to be representative of control subjects in our region (Chinnery et al., 2007); and (3) a local cohort of healthy older subjects (n = 93, 35% male; mean age 69, standard deviation = 8.5).

Mitochondrial haplogroup data were available for 85.8% (696/811) of those with RFI available and 91.4% (477/552) of those with FFS available. These were the samples used in the principal analyses. Linear regression was used to determine the relationship between mtDNA haplogroups and RFI, and ordinal logistic regression was used to determine the relationship between mtDNA haplogroups and FFS, both before and after controlling for sex, years of education, and smoking status. A count of chronic diseases was used as an additional control for the FFS. The relationship between mtDNA haplogroups and survival was determined by Cox proportional hazards analysis, both before and after controlling for sex, total cholesterol, body mass index, hypertension, diabetes, ethnicity, and smoking status. The median follow-up period was 58 months during which 336 deaths occurred.

3. Results

The overall frequency distribution of mtDNA haplogroups in the incident Newcastle 85+ cohort was compared with the birth cohort (p = 344), mid-age cohort (p = 2889), and old-age cohort (p = 93) (Table 1). The only significant difference in distributions was for the local older cohort that differed from each of the other cohorts in the “other” haplogroup category only.

There was no significant association between mtDNA haplogroups and frailty (RFI or FFS) before and after controlling for the potential confounding variables (Tables 2 and 3). Although we observed an association between haplogroup X and increased mortality (p = 0.025), this was not apparent after controlling for total cholesterol, body mass index, hypertension, diabetes, ethnicity, and smoking status (Table 4). Likewise, the trend toward reduced mortality associated with haplogroup K (p = 0.041), which remained after controlling for other variables (p = 0.023), did not withstand correction for the multiple haplogroups under investigation.

4. Discussion

We found no robust evidence of an association between mtDNA haplogroups and either frailty or survival beyond age 85 or any

Table 2

RFI and mitochondrial haplogroup—regression coefficients (unstandardized) for square root—transformed RFI by mitochondrial haplogroup*

| Haplogroup | Model 1, unstandardized regression coefficient (95% confidence interval) | Model 1, p value | Model 2, unstandardized regression coefficient (95% confidence interval) | Model 2, p value | Model 3, unstandardized regression coefficient (95% confidence interval) | Model 3, p value |
|-----------|-------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------|-----------------|
| H         | 0.015 (-0.003 to 0.034)                                                 | 0.101           | 0.017 (-0.001 to 0.036)                                                  | 0.065           | 0.013 (-0.006 to 0.031)                                                   | 0.175           |
| Reference | Reference                                                               | Reference       | Reference                                                                 | Reference       | Reference                                                                 | Reference       |
| T         | -0.006 (-0.037 to 0.024)                                                | 0.684           | -0.009 (-0.040 to 0.021)                                                 | 0.536           | -0.007 (-0.036 to 0.023)                                                 | 0.663           |
| Non-T     | -0.016 (-0.045 to 0.014)                                                | 0.300           | -0.014 (-0.043 to 0.015)                                                 | 0.338           | -0.011 (-0.040 to 0.018)                                                 | 0.455           |
| J         | -0.009 (-0.035 to 0.016)                                                | 0.481           | -0.009 (-0.034 to 0.016)                                                 | 0.488           | -0.008 (-0.033 to 0.017)                                                 | 0.526           |
| Non-J     | -0.033 (-0.068 to 0.003)                                                | 0.069           | -0.033 (-0.068 to 0.002)                                                 | 0.064           | -0.029 (-0.064 to 0.007)                                                 | 0.112           |
| U         | -0.060 (-0.008 to 0.128)                                                | 0.083           | 0.057 (-0.010 to 0.124)                                                  | 0.098           | 0.053 (-0.014 to 0.120)                                                  | 0.122           |
| Non-U     | Reference                                                               | Reference       | Reference                                                                 | Reference       | Reference                                                                 | Reference       |
| K         | -0.015 (-0.040 to 0.007)                                                | 0.585           | 0.012 (-0.043 to 0.066)                                                  | 0.675           | 0.018 (-0.037 to 0.072)                                                  | 0.523           |
| Non-W     | 0.052 (-0.022 to 0.126)                                                 | 0.170           | 0.047 (-0.026 to 0.120)                                                  | 0.206           | 0.051 (-0.022 to 0.123)                                                  | 0.169           |
| I         | -0.019 (-0.068 to 0.031)                                                | 0.461           | -0.020 (-0.069 to 0.029)                                                 | 0.424           | -0.020 (-0.069 to 0.028)                                                 | 0.410           |
| Non-V     | Reference                                                               | Reference       | Reference                                                                 | Reference       | Reference                                                                 | Reference       |

Key: RFI, Rockwood frailty index.

* Linear regression models were fitted with RFI (square root transformed to give adequate model fit) as the dependent variable and mitochondrial haplogroup as the independent variable. Seven binary variables were created of “in haplogroup H” versus “not in haplogroup H” type, and 7 models were run entering each binary variable separately. Model 1 is adjusted, model 2 adjusted for sex, and model 3 adjusted for sex, education, and smoking status.
informative biomarker of aging (Martin-Ruiz et al., 2011), and the overall distribution of mtDNA haplogroups closely resembled ethnically matched cohorts from 3 different younger age groups. Our findings do not support a role for mtDNA in promoting healthy aging or longevity. The absence of an age-associated stratification of mtDNA haplogroups is in agreement with previous findings in large European cohorts (Benn et al., 2008; Dato et al., 2004). On the other hand, our findings contrast with the results of several smaller European (De Benedictis et al., 1999; Dominguez-Garrido et al., 2009; Ivanova et al., 1998; Niemi et al., 2003; Ross et al., 2001) and Far-Eastern studies (Feng et al., 2011; Zhang et al., 2003). Although it is conceivable that these geographic differences reflect different environmental constraints, or ethnic differences in the nuclear genetic background, it is perhaps more likely that the relatively small size of these study groups led to false-positive associations because mtDNA haplogroup studies are particularly sensitive to population stratification. In keeping with this, none of the previously reported positive findings have been replicated directly, and it is not clear why a particular haplogroup would be associated with longevity in one context and not the other. Likewise, we were unable to replicate previous findings of a gender-specific association with aging. If present, such an association would be difficult to explain mechanistically.

Although we cannot exclude the possibility that a larger study cohort would reveal an association between mtDNA and longevity and/or healthy aging phenotypes, our findings of a lack of an association with 2 sensitive and reliable measures of frailty and no direct evidence of an effect on survival suggest that any contribution from mtDNA would be modest at best. Our results, therefore, turn the spotlight away from mtDNA back to the nuclear genome, in the search for genes predisposing to longevity and healthy aging.

Table 3
FFS and mitochondrial haplogroup—odds ratio (95% confidence interval) of being in a higher Fried a status (pre-frail or frail versus pre-frail) by mitochondrial haplogroup

| Haplogroup | Model 1, odds ratio (95% confidence interval) | Model 1, p value | Model 2, odds ratio (95% confidence interval) | Model 2, p value | Model 3, odds ratio (95% confidence interval) | Model 3, p value |
|------------|---------------------------------------------|-----------------|---------------------------------------------|-----------------|---------------------------------------------|-----------------|
| H          | 1.05 (0.73–1.50)                            | 0.790           | 1.10 (0.77–1.57)                            | 0.608           | 1.04 (0.71–1.53)                            | 0.832           |
| Non-H      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| T          | 1.10 (0.61–1.96)                            | 0.752           | 0.93 (0.52–1.68)                            | 0.815           | 0.80 (0.43–1.51)                            | 0.498           |
| Non-T      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| J          | 0.72 (0.41–1.27)                            | 0.262           | 0.74 (0.42–1.31)                            | 0.305           | 0.99 (0.54–1.81)                            | 0.968           |
| Non-J      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| U          | 0.95 (0.59–1.52)                            | 0.816           | 0.95 (0.59–1.52)                            | 0.820           | 0.85 (0.51–1.41)                            | 0.526           |
| Non-U      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| K          | 0.66 (0.33–1.32)                            | 0.248           | 0.70 (0.35–1.37)                            | 0.293           | 0.79 (0.38–1.64)                            | 0.532           |
| Non-K      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| X          | 4.45 (0.91–21.71)                           | 0.065           | 4.32 (0.87–21.52)                           | 0.074           | 3.64 (0.68–19.61)                           | 0.132           |
| Non-X      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| W          | 2.58 (0.88–7.57)                            | 0.084           | 2.30 (0.78–6.81)                            | 0.131           | 2.90 (0.89–9.49)                            | 0.078           |
| Non-W      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| I          | 0.95 (0.10–9.10)                            | 0.967           | 0.89 (0.09–8.53)                            | 0.918           | 1.14 (0.11–11.78)                           | 0.913           |
| Non-I      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |
| V          | 1.20 (0.43–3.32)                            | 0.729           | 1.29 (0.46–3.58)                            | 0.630           | 1.20 (0.38–3.71)                            | 0.757           |
| Non-V      | Reference                                   |                  | Reference                                   |                  | Reference                                   |                  |

Key: FFS, Fried frailty status.

* Ordinal logistic regression models were fitted with Fried status as the dependent variable and mitochondrial haplogroup as the independent variable. Seven binary variables were created of “in haplogroup H” versus “not in haplogroup H” type, and 7 models were run entering each binary variable separately. Model 1 is unadjusted, model 2 adjusted for sex only, and model 3 adjusted for sex, years of education, smoking status, and count of chronic diseases.

Table 4
Hazard ratios for mortality by mitochondrial haplogroup

| Haplogroup | Model 1, hazard ratio (95% confidence interval) | Model 1, p value | Model 2, hazard ratio (95% confidence interval) | Model 2, p value |
|------------|---------------------------------------------|-----------------|---------------------------------------------|-----------------|
| H          | 1.10 (0.89–1.36)                            | 0.380           | 1.04 (0.82–1.31)                            | 0.748           |
| Non-H      | Reference                                   |                  | Reference                                   |                  |
| T          | 1.00 (0.70–1.43)                            | 0.988           | 1.04 (0.72–1.50)                            | 0.852           |
| Non-T      | Reference                                   |                  | Reference                                   |                  |
| J          | 0.92 (0.65–1.50)                            | 0.625           | 0.95 (0.66–1.36)                            | 0.762           |
| Non-J      | Reference                                   |                  | Reference                                   |                  |
| U          | 0.97 (0.72–1.31)                            | 0.841           | 1.13 (0.83–1.55)                            | 0.425           |
| Non-U      | Reference                                   |                  | Reference                                   |                  |
| K          | 0.61 (0.38–0.98)                            | 0.041           | 0.52 (0.30–0.91)                            | 0.023           |
| Non-K      | Reference                                   |                  | Reference                                   |                  |
| X          | 2.05 (1.09–3.86)                            | 0.025           | 1.91 (0.96–1.83)                            | 0.066           |
| Non-X      | Reference                                   |                  | Reference                                   |                  |
| W          | 0.85 (0.42–1.72)                            | 0.652           | 0.90 (0.42–1.92)                            | 0.790           |
| Non-W      | Reference                                   |                  | Reference                                   |                  |
| I          | 0.99 (0.41–2.38)                            | 0.973           | 0.71 (0.26–1.93)                            | 0.506           |
| Non-I      | Reference                                   |                  | Reference                                   |                  |
| V          | 1.28 (0.75–2.19)                            | 0.360           | 1.22 (0.68–2.19)                            | 0.497           |
| Non-V      | Reference                                   |                  | Reference                                   |                  |

Bold text indicates p < 0.05.

* Seven binary variables were created of “in haplogroup H” versus “not in haplogroup H” type, and 7 models were run entering each binary variable separately. Model 1 is unadjusted and model 2 is adjusted for sex, ethnicity, total cholesterol, body mass index, hypertension, diabetes, and smoking.

Disclosure statement

The authors report no conflicts of interest.

The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere, and will not be submitted elsewhere while under consideration at Neurobiology of Aging. All authors have reviewed the contents of the manuscript being submitted, approved of its contents, and validated the accuracy of the data.

Ethical approval for the study is in place.

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References

Beekman, M., Blanche, H., Perola, M., Hervonen, A., Bezrukov, V., Sikora, E., et al., 2013. Genome-wide linkage analysis for human longevity: genetics of Healthy Aging Study. Aging Cell 12, 184–193.

Benn, M., Schwartz, M., Nordestgaard, B.G., Tybjaerg-Hansen, A., 2008. Mitochondrial haplogroups: ischemic cardiovascular disease, other diseases, mortality, and longevity in the general population. Circulation 117, 2492–2501.

Chinnery, P.F., Mowbray, C., Patel, S.K., Elson, J.L., Sampson, M., Hitman, G.A., McCarthy, M.I., Hattersley, A.T., Walker, M., 2007. Mitochondrial DNA haplogroups and type 2 diabetes: a study of 897 cases and 1010 controls. J. Med. Genet. 44, e80.

Collerton, J., Davies, K., Jagger, C., Kingston, A., Bond, J., Eccles, M.P., et al., 2009. Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. BMJ 339, b4904.

Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C.M., Isaacs, J., Kolenda, C., et al., 2012. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ study. Mech. Ageing Dev. 133, 456–466.

Courtney, M.D., Gilbert, J.R., Jiang, L., Cummings, A.C., Gallins, P.J., Gaywood, L., et al., 2012. Mitochondrial haplogroup X is associated with successful aging in the Amish. Hum. Genet. 131, 201–208.

Dato, S., Passarino, G., Rose, G., Altomare, K., Bellizzi, D., Mari, V., et al., 2004. Association of the mitochondrial DNA haplogroup J with longevity is population specific. Eur. J. Hum. Genet. 12, 1080–1082.

De Benedictis, G., Rose, G., Carriero, G., De Luca, M., Falcone, E., Passarino, G., et al., 1999. Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. Faseb J. 13, 1532–1536.

Domínguez-Garrido, E., Martínez-Redondo, D., Martín-Ruiz, C., Gomez-Duran, A., Ruiz-Pesini, E., Madero, P., et al., 2009. Association of mitochondrial haplogroup J and mtDNA oxidative damage in two different North Spain elderly populations. Biogerontology 10, 435–442.

Elliott, H.R., Samuels, D.C., Eden, J.A., Retlon, C.L., Chinnery, P.F., 2008. Pathogenic mitochondrial DNA mutations are common in the general population. Am. J. Hum. Genet. 83, 254–260.

Feng, J., Zhang, J., Liu, M., Wan, G., Qi, K., Zheng, C., et al., 2011. Association of mtDNA haplogroup F with healthy longevity in the female Chuang population, China. Exp. Gerontol. 46, 987–993.

Finnila, S., Hassenk, L.E., Ala-Kokko, L., Majamaa, K., 2000. Phylogenetic network of the mtDNA haplogroup U in Northern Finland based on sequence analysis of the complete coding region by conformation-sensitive gel electrophoresis. Am. J. Hum. Genet. 66, 1017–1026.

Fried, L.P., Xue, Q.L., Cappola, A.R., Ferrucci, L., Chaves, P., Varadhan, R., et al., 2009. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J. Gerontol. A Biol. Sci. Med. Sci. 64, 1049–1057.

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

Kirkwood, T.B., Cordell, H.J., Finch, C.E., 2011. Speed-bumps ahead for the genetics of later-life diseases. Trends Genet. 27, 387–388.

Martin-Ruiz, C., Jagger, C., Kingston, A., Collerton, J., Catt, M., Davies, K., et al., 2011. Assessment of a large panel of candidate biomarkers of ageing in the Newcastle 85+ study. Mech. Ageing Dev. 132, 496–502.

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

Niemi, A.K., Molanen, J.S., Tanaka, M., Hervonen, A., Hurme, M., Lehtimaki, T., et al., 2005. A combination of three common inherited mitochondrial DNA polymorphisms promotes longevity in Finnish and Japanese subjects. Eur. J. Hum. Genet. 13, 166–170.

Rockwood, K., Mitnitski, A., 2007. Frailty in relation to the accumulation of deficits. J. Gerontol. A Biol. Sci. Med. Sci. 62, 722–727.

Ross, O.A., McCormack, R., Curran, M.D., Duguid, R.A., Barnett, Y.A., Rea, I.M., et al., 2001. Mitochondrial DNA polymorphism: its role in longevity of the Irish population. Exp. Gerontol. 36, 1161–1178.

Schon, E.A., DiMauro, S., Hincman, M., 2012. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat. Rev. Genet. 13, 878–890.

Tanaka, M., Gong, J., Zhang, J., Yamada, Y., Borgia, H., Yagi, K., 2000. Mitochondrial genotype associated with longevity and its inhibitory effect on mutagenesis. Mech. Ageing Dev. 116, 65–76.

Tanaka, M., Gong, J.-S., Zhang, J., Yoned, M., Yagi, K., 1998. Mitochondrial genotype associated with longevity. Lancet 351, 185–186.

Torrone, A., Huoponen, K., Francalacci, P., Pirozzi, M., Morelli, L., Scuozari, R., et al., 1996. Classification of European mtDNAs from an analysis of three European populations. Genetics 144, 1835–1850.

Yang, X., Wang, X., Yao, H., Deng, J., Jiang, Q., Guo, Y., et al., 2012. Mitochondrial DNA polymorphisms are associated with the longevity in the Guangxi Bama population. Exp. Gerontol. 47, 912–9131.

Zhang, J., Asin-Cayuela, J., Fish, J., Michikawa, Y., Bonafe, M., Olivieri, F., et al., 2003. Strikingly higher frequency in centenarians and twins of mtDNA mutation causing remodeling of replication origin in leukocytes. Proc. Natl. Acad. Sci. U.S.A. 100, 1116–1121.