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Heritability of Telomere Length in a Study of Long-Lived Families

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Abstract

Chromosomal telomere length shortens with repeated cell divisions. Human leukocyte DNA telomere length (LTL) determined has been shown to shorten during aging. LTL shortening has correlated with decreased longevity, dementia, and other age-associated processes. Since LTL varies widely between individuals in a given age group, it has been hypothesized to be a marker of biological aging. However, the principal basis for the variation of human LTL has not been established, although various studies have reported heritability. Here we use a family-based study of longevity to study heritability of LTL in 3037 individuals. We show that LTL is shorter in older

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The authors have no actual or potential conflicts of interest with respect to this work. The Institutional Review Boards at each of the institutions in the US and the regional ethical committee in Denmark reviewed and approved this project.

individuals, and in males, and has a high heritability (overall $h^2 = 0.54$). In the offspring generation, who are in middle-life, we find an ordinal relationship: persons more-closely-related to elderly probands have longer LTL than persons less-closely-related, who nonetheless have longer LTL than unrelated spouses of the offspring generation. These results support a prominent genetic underpinning of LTL. Elucidation of such genetic bases may provide avenues for intervening in the aging process.

Keywords

Telomere; Heritability; Longevity; Aging

1. Introduction

Chromosomal leukocyte telomere length may relate to successful aging. Telomeres are repetitive DNA consisting of hundreds of concatenated TTAGGG hexanucleotide sequences, located at the end of each human chromosome. Telomeres allow for preservation of the genome during replication and division. However, in most cells telomere sequences shorten with each cell replication to the extent that they are not repaired by telomerase, an enzymatic activity of variable presence in some cell types (Hodes et al., 2002). On a cellular basis, reduction in telomere length is an indicator of cellular aging. Gradual loss of telomeric DNA in dividing somatic cells can contribute to replicative senescence or apoptosis (Benetos et al., 2001 ; Blackburn, 2000 ; Linskens et al., 1995 ; Martin-Ruiz et al., 2004 ; von Zglinicki, 1998 ; Zou et al., 2004). On an organismal basis, it is established that LTL shortens with age in human populations and may serve as a marker of biological aging (Cawthon et al., 2003 ; Fitzpatrick et al., 2011 ; Honig et al., 2012 ; Honig et al., 2006 ; Martin-Ruiz et al., 2006 ; Sanders et al., 2012).

Human life span relates to leukocyte telomere length (LTL) in a number of population studies, with greater longevity associated with longer LTL (Cawthon et al., 2003 ; Fitzpatrick et al., 2011 ; Honig et al., 2012 ; Honig et al., 2006 ; Martin-Ruiz et al., 2006). However, some studies have not observed this association (Bischoff et al., 2006 ; Martin-Ruiz et al., 2005 ; Njajou et al., 2009), and some have proposed that LTL may relate more to “healthy aging” than to survival (Njajou et al., 2009 ; Sanders et al., 2012 ; Terry et al., 2008). LTL is generally longer in women than men (Barrett and Richardson, 2011 ; Honig et al., 2012 ; Shaffer et al., 2012 ; Zhu et al., 2011), but this could be related to either healthy aging or survival.

LTL has been reported to have heritability of varying degrees, up to 78%, in studies of different population groups and twin cohorts (Andrew et al., 2006 ; Bischoff et al., 2005 ; Broer et al., 2013 ; Jeanclos et al., 2000 ; Nordfjall et al., 2005 ; Nordfjall et al., 2010 ; Slagboom et al., 1994 ; Vasa-Nicotera et al., 2005). Some studies have suggested a greater degree of heritability from fathers than mothers, while others have found the opposite, or no such relationship. Recent genome-wide linkage and association studies have reported candidate loci and gene SNPs (Andrew et al., 2006 ; Codd et al., 2010 ; Deelen et al., 2011 ; Soerensen et al., 2012 ; Vasa-Nicotera et al., 2005). Population-based studies of LTL may be affected by differential effects on “health” and survival. Here we make use of data collected

from a multigenerational family-based study of long-lived persons to examine the relation of LTL to longevity. We examine the heritability of LTL in these participants specifically selected for membership in families with longevity - and examine whether members of the offspring generation of the Long Life Family Study (LLFS) have longer LTL than their similarly aged “married-in” spouses, at ages before substantial mortality occurred. We hypothesized that LTL would be heritable, and that offspring of Long Life Family Study members would have longer telomeres than similarly aged peers.

2. Methods

2.1 Study population

The LLFS study is funded by the National Institute on Aging, and involves collaboration with the Center for Medicare and Medicaid Services via an Inter-Agency Agreement, a Data Management and Coordinating Center at Washington University St. Louis, a Laboratory Coordinating Site at the University of Minnesota, and four Clinical Centers: Boston University, Columbia University, the University of Pittsburgh, and the University of Southern Denmark. Long-lived individuals, their siblings and their offspring were recruited, and a referent group consisting of the spouses, primarily of the offspring generation, was also recruited and examined. In the US, recruitment involved mailings to elderly people (at least 79 years old in the initial phase, then in later phase, people at least 89 years old) who on January 1, 2005 had neither end-stage renal disease nor were in a hospice program, but did live within 3 hours driving distance of one of the three US study centers. There was also community-recruitment using web-based media, newspaper advertisements, and community presentations. In Denmark, the Danish National Register was used to identify individuals age 90 and above during the study recruitment period (Pedersen et al., 2006), and then archives were searched to locate the parents of the elderly individuals in order to identify potentially eligible sibships, who were then contacted regarding participation in the LLFS using criteria parallel to those used in the United States. Overall, 32.9% of the offspring generation were Danish. The Institutional Review Boards at each of the institutions in the US and the regional ethical committee in Denmark reviewed and approved this project.

2.2 Eligibility and Enrollment

The Family Longevity Selection Score (FLoSS) was developed to rank families according to their collective survival exceptionality (Sebastiani et al., 2009). Probands were screened for evidence of familial longevity using the FLoSS, which scored family longevity using birth-year cohort survival probabilities of the proband and siblings (Sebastiani et al., 2009). Families were eligible if they had a FLoSS score of 7 or more, the proband and at least one living sibling were able to give informed consent and willing to participate in the baseline in-person interview and examination, and either the proband or a sibling had a living offspring willing to participate. A minimum of two siblings and one offspring was required. Spouses, primarily in the offspring generation, were recruited to serve as comparison controls from the same population, but not selected for familial longevity. Spouse controls provide a similarly aged comparison group and are employed to adjust for characteristics of individuals within a family, which are likely to be correlated. Prior to examination, all

enrollees provided written informed consent (which in a few cases was by proxy, with participant assent).

2.3 Study Examinations

Examinations characterized key intermediate phenotypes of longevity, including presence or absence of major chronic diseases, risk factors, and assessment of physical and cognitive function. Interviews and examinations were conducted in the home with portable equipment by trained research assistants using a standardized protocol. Research staff traveled to examine families and family members outside of the field center regions (about 20% of the US study centers sample) when the family was highly exceptional (FLoSS ≥15) or to enroll additional family members who resided outside of the field center regions. If some US cases, an in-person visit was not feasible, and a comprehensive telephone interview was conducted, with blood sample obtained by an outside service provider. Demographic data included date of birth, which was validated by birth certificate and/or correlation with U.S. census records. Sex, race, ethnicity, and education (years completed) were ascertained by self or proxy report. Past and current physical activity levels, smoking history and history of alcohol use were ascertained by questionnaire. Past medical history was defined by self-reported diagnoses provided by physicians. Physical examinations included height, weight, vital signs, forced vital capacity, ankle arm blood pressure index, and tests of physical and cognitive function. Blood was collected for DNA and plasma.

2.4 DNA samples

Usable blood DNA was obtained at baseline visit for the proband generation, and for 96.1% of the offspring generation, including 95.8% (2270/2371) of offspring and 96.8% (767/793) of controls. DNA was extracted from the white blood cells (WBC) from frozen buffy coat from EDTA-anticoagulated (and in some cases citrate-anticoagulated) whole blood using a salt-precipitation method (Gentra Puregene®, Qiagen Inc., Germantown, MD) and stored at -80C as coded samples. In this study, only DNA isolated from blood, not saliva, was used.

2.5 Measurement of Telomere Length

DNA samples were processed by laboratory personnel blinded to participant characteristics. Average telomere length was determined by a modification of a method developed by Cawthon and colleagues (Honig et al., 2012 ; Shaffer et al., 2012).(Cawthon, 2002 2002; Cawthon et al., 2003) Real-time PCR was performed using a CFX384 thermocycler (Biorad, Richmond, CA). The assay method was optimized for use of both telomere (T) and single copy gene (S) amplifications on the same 384-well plate, with standard reference DNA sample on each plate. Test DNA samples each underwent two triplicate PCR reactions, with use of “calibrator samples” for correction for inter-plate variability. Amplification primers for telomeres included T_{for}: 5′-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3′ and T_{rev}: 5′-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3′, and for single copy gene (beta-globin) S_{for} 5′-GCTTCTGACACAACTGTGTTCACTAGC-3′ and S_{rev} 5′-CACCAACTTCATCCACGTTCACC-3′. Thermocycling parameters were 95°C x10min activation, followed by 34 cycles of 95°C x15sec, and 55°C x120sec. For this study, our assay coefficient of variance averaged 4.8% ± 1.8% (range 0.3 – 10.8% on a per sample

basis). Using the calibrators as standards, T/S ratio was converted to base-pairs (bp) LTL by use of the linear regression formula: bp=(1,585*T/S ratio)+3,582, obtained by co-analysis of selected DNA samples using both PCR and terminal restriction fragment (non-radioactive *Telo**TAGGG* Telomere Length, Roche Diagnostics, Mannheim, Germany) methods (correlation coefficient r = 0.90). The use of the calibrators makes these base-pair measurements comparable to others from our laboratory (Honig et al., 2012 ; Shaffer et al., 2012).

2.6 Heritability Analysis

We computed additive genetic heritability of leukocyte telomere length using a maximum-likelihood variance-component model as implemented in SOLAR (Almasy and Blangero, 1998; Blangero and Almasy, 1997). This model uses leukocyte telomere length measures from all family members, including those of both proband and offspring generations to estimate heritability as a proportion of the additive genetic variance over the total genetic and environmental variance. For the present study, heritability estimates were computed using proband and offspring generations, while adjusting for multiple potential confounders, including age, sex, education, site, generation, smoking (ever vs. never), alcohol consumption (yes vs. no), marital status (widowed/divorced vs. never married vs. married), a history of heart disease (yes/no) and diabetes (yes/no), and 20 principal components (the “full model”). In this full model, covariates were included that were significant at $p<0.05$, including age, sex, education, field center site, smoking status, alcohol consumption status, marital status, and history of heart disease. Even though not all three indicator variables for center site were significant, we forced the site variable into the model. In addition to the full model, with extensive demographic and risk factor confounders, we repeated heritability analysis, with a “simple model,” adjusting only for demographic confounders. This was performed to address the possibility that by adjusting for both demographic and environmental risk factors, there might be an underestimate of environmental variance associated with LTL. Further assessment of inheritance of leukocyte telomere length in families, included estimation of separate heritabilities, conditional on sex of parents (proband generation), and sex of offspring, as shown in Table 3. Since the life expectancy for men is lower than for women, elderly males at a given age represent a more extreme end of the age distribution, than females. To assess the influence of father’s telomere length, we used leukocyte telomere length for all family members from the nuclear family after treating mother’s telomere length as missing. Similarly, to assess the influence of mother’s telomere length, we used leukocyte telomere length for all, excluding father’s telomere length measure.

2.7 Other Statistical Procedures

Analysis was performed to address the question of whether LTL of offspring were longer LTL of similarly aged spouses. The analysis was performed using SPSS version 19.0, restricting the sample to the offspring generation and the enrolled spouses of these individuals. Preliminary analyses used chi-square tests for categorical variables and Student’s t test and analysis of variance for continuous variables to compare LTL and demographic characteristics of LLFS offspring with spouse controls. Further analyses then used logistic and linear regression procedures to compare LTL among the first-degree (sons

and daughters) and second-degree (nieces and nephews) relatives in the offspring generation compared with their spouse controls, adjusting for age, and education. We used the logistic regression procedure in Generalized Estimating Equations (GEE), clustering on families, to compare the likelihood of being in the highest tertile of LTL in sons and daughters or nieces and nephews of probands to the likelihood of being in the highest tertile of LTL in similarly aged spouses. Covariates included age, sex, and education. GEE adjusts for the relatedness of the LLFS offspring as well as the spouse control group by treating family membership as a cluster. GEE considers multiple measures per individual and the possibility that the characteristics of family members are correlated by both shared genetics and shared environment. Furthermore, since telomere length is somewhat longer in females than males, sex-stratified tertiles were used as described below, and separate analyses were performed stratified by sex.

3. Results

3.1 Characteristics of LLFS offspring generation

This study used all members of the offspring generation (N = 3,164) who had blood DNA measurements of LTL (N = 3,040) and were assessed. This includes 2272 offspring, of whom 724 were sons and daughters and 1,548 were nephews and nieces; there were 768 spouse-controls of this generation (Table 1). Overall 1667 (54.8%) of participants were women, and this female predominance was somewhat higher among children (sons and daughters) of probands (60.8%), than among second-degree (nephews and nieces) relatives (56.0%), and spouse controls (46.9%). Mean age at assessment was similar for sons and daughters (60.8 yr), nephews and nieces (59.9 yr), and spouse controls (60.5 yr). The average number of years of education did not differ among offspring and controls, but was slightly higher in sons and daughters than in nephews and nieces (Table 1). Ethnicity was more than 99% white in all groups; a total of only 15 of the 3040 participants were non-white. For the entire offspring generation, mean LTL was longer in offspring than controls, and longer in sons and daughters than in nephews and nieces. However, because LTL relates to both sex and age, statistical analyses below were performed adjusting for age and sex as covariates.

3.2 Telomere length relates to age and sex

Linear regression analysis of LTL with age, adjusting for sex and education revealed that LTL was shorter in older participants, and in males (Figure 1), with a decrease in 14.5 ± 1.1 bp per year of age ($p < 0.000001$), and average difference of 46.9 ± 18.8 bp greater TL in females than males ($p = 0.01$). There was also a significant effect of education with an average 14.5 ± 3.0 bp increase in LTL for each year of education ($p < 0.0001$). In Figure 1, it can be seen that the longer LTL in males was reflected in each decade of age between 40 and 80 years (while there were too few offspring generation below age 40 or above age 80 to make conclusions at this extremes).

3.3 Telomere length relates to membership in long-lived families

Raw unadjusted correlations revealed modest correlation of LTL among arbitrary paired siblings within a family ($r = 0.298$), and no correlation among arbitrary paired spouse

controls within a family (r=0.013). Logistic regression analyses, with appropriate covariates below, were performed to determine the relationship of LTL to family status (Table 2). The model included adjustments for age, sex and education. Membership in a long-lived family, as an offspring, was associated with an increased likelihood of being a in a higher tertile of telomere length, compared to those married into the offspring generation. This was true in a graded fashion between tertiles (Table 2). Furthermore, within the offspring relatives, first-degree relatives of the proband (sons and daughters) had longer LTL than did second-degree relatives (nieces and nephews), although both were longer than in spouse controls. In sex-stratified analyses, these effects were seen both in men and women (not shown).

3.4 Telomere length heritability estimates

The overall heritability of leukocyte telomere length estimated using SOLAR, was high: 0.54 (SE = 0.034) in this 2-generation cohort. Because of the sex-differences in TL, the plausibility of possible “epigenetic transmission” of telomere length, and prior reports suggesting the possibility of differential heritability of TL from maternal or paternal sources, we examined the heritability separately by sex of both older and younger generation (Table 3). We found that heritability estimates did not differ markedly when conditional on male or female parents. Heritability estimates for male parents to their offspring were not significantly higher than those for female parents (0.67 vs. 0. 0.61 respectively; t = 0.44, p >0.05). Similarly, heritability from male parents to all offspring was 0.67 while from male parents to male offspring was 0.65 and to female offspring was 0.62. When heritability estimates were computed conditional on female parents, estimates were slightly lower. Heritability estimates for female parents to all offspring was 0.61 while female parents to male offspring was 0.57 and to female offspring was 0.53, but none of these gender differences were statistically significant. When the analyses were all repeated, adjusting only for demographic confounders (the “simple model” in Table 3), to reduce potential overcorrection as discussed in the methods section, heritability estimates were lowered only slightly, but still did not show significant differences. Because of the possibility that sibling correlations might affect this analysis, the entire analyses in both full model and simple model were also run using only a single randomly chosen offspring (either male or female for each analysis). Such analyses revealed slightly lower heritability estimates of 0.40 – 0.63 versus the estimates in Table 3 of 0.53 – 0.67, and more noise (higher ratios of SE to h^2 of 0.09 – 0.21 vs 0.07 – 0.11). However, the overall heritabilities were still each highly significant, and independent of gender effects. Thus while heritability of LTL was high, there were no significant differences between heritability from males or females, or whether to males or females of the younger generation.

4. Discussion

We employed a family based study to examine the heritability of telomere length, and the relation of telomere length to membership in long lived families. Prior family-based studies have suggested that telomere length is heritable (Andrew et al., 2006; Bischoff et al., 2005; Jeanclos et al., 2000; Slagboom et al., 1994; Vasa-Nicotera et al., 2005), but the relationship of telomere length to longevity is inconsistent, with some studies showing a relationship of LTL to survival, (Cawthon et al., 2003 ; Fitzpatrick et al., 2011 ; Honig et al., 2012 ; Honig

et al., 2006 ; Martin-Ruiz et al., 2006), while other studies found a relationship of LTL with healthy aging but not with survival (Njajou et al., 2009 ; Sanders et al., 2012 ; Terry et al., 2008). This study was designed to avoid confounding of "healthy aging" effects with "survival" effects. By examining LTL in the offspring generation, before significant mortality occurred, "survival" effects should be avoided. Thus, this study provides evidence for effects of LTL of belonging to a "long-lived family", and also allows assessment of heritability by comparing the first-degree relatives (sons and daughters), with second-degree relatives (nieces and nephews), as well as with unrelated spouse-controls.

Among the total group of participants, our results are consistent with prior studies that show that older individuals have shorter LTL. This study also confirms that men have shorter LTL than women (Barrett and Richardson, 2011 ; Shaffer et al., 2012; Zhu et al., 2011), suggesting that men are on average "biologically older" than women at similar chronological ages. In this cohort, heritability estimates for LTL are over 50%. We compared mean telomere length and the likelihood of being in the longest tertile of telomere length among nieces and nephews, sons and daughters, and unrelated spouses, in these families selected for exceptional longevity in the proband (older) generation. First-degree relatives of probands from families selected for exceptional longevity had longer LTL than the second-degree relatives, and these in turn had longer LTL than their married-in spouses. This may be consistent with overall effects of telomere length marking effective biological age, and with heritability of more favorable, "healthier," biological aging.

Prior studies have demonstrated heritability of LTL, although estimates have varied widely from about 30% to 80% (Al-Attas et al., 2012 ; Andrew et al., 2006 ; De Meyer et al., 2007 ; Jeanclos et al., 2000 ; Nordfjall et al., 2005 ; Nordfjall et al., 2010 ; Slagboom et al., 1994 ; Vasa-Nicotera et al., 2005 ; Wong et al., 2011). In addition, some studies have suggested a uniparental inheritance effect, with stronger inheritance from father to child (Njajou et al., 2007 ; Nordfjall et al., 2010) or mother to child (Broer et al., 2013). In this study we confirm significant heritability on the order of 60%, but do not confirm a different heritability from mother versus father, or to male versus female offspring. We conclude that there may not be a paternal or maternal inheritance effect, but the failure to observe such an effect difference might possibly relate to differences in populations studied, or in particular to the selection for longevity in this family-based study.

Strengths of this study include that it examines telomere length in a large number of individuals and that these individuals are from long-lived families or are married-in spouse controls. The study shows telomere length differences in the offspring generation, consistent with an inherited tendency towards slower biological aging – whether due to genetic factors, environmental influences, or better health choices. Limitations of the study, include: (a) that this is an ethnically homogenous selected sample (nearly all white, although it includes sites in both US and Denmark) that may not be generalizable to the population at large; (b) that only a single DNA sample for TL measurement was obtained from each individual, so neither telomerase measurements are available, nor measurement of longitudinal change; (c) that it is not possible to be certain that all familial effects are truly genetically inherited, versus related to common environmental variables (for example, not only siblings, but even genetically unrelated spouses share environment); and (d) that it is possible that LTL

differences reflect higher proportions of particular leukocyte subtypes, perhaps reflecting medical conditions, rather than “biological aging”. However, this study does lend support to the hypothesis that telomere length is heritable, and that, keeping in mind the above caveats, longer telomeres might reflect a slower biological aging process. This study supports the possibility of further investigations examining the genetic factors responsible for telomere length and longevity (Lee et al., 2014). Ultimately, identification of genes and gene products that might be involved in biological aging might not only contribute to increased knowledge regarding aging, but also to the possibility of interventions to slow biological aging, perhaps interventions ultimately based on telomere maintenance.

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HIGHLIGHTS

- We examine heritability of Leukocyte telomere length in a family-based study.
- Telomere length has a high heritability (overall $h^2 = 0.54$).
- Heritability does not seem to depend on maternal or paternal inheritance factors.

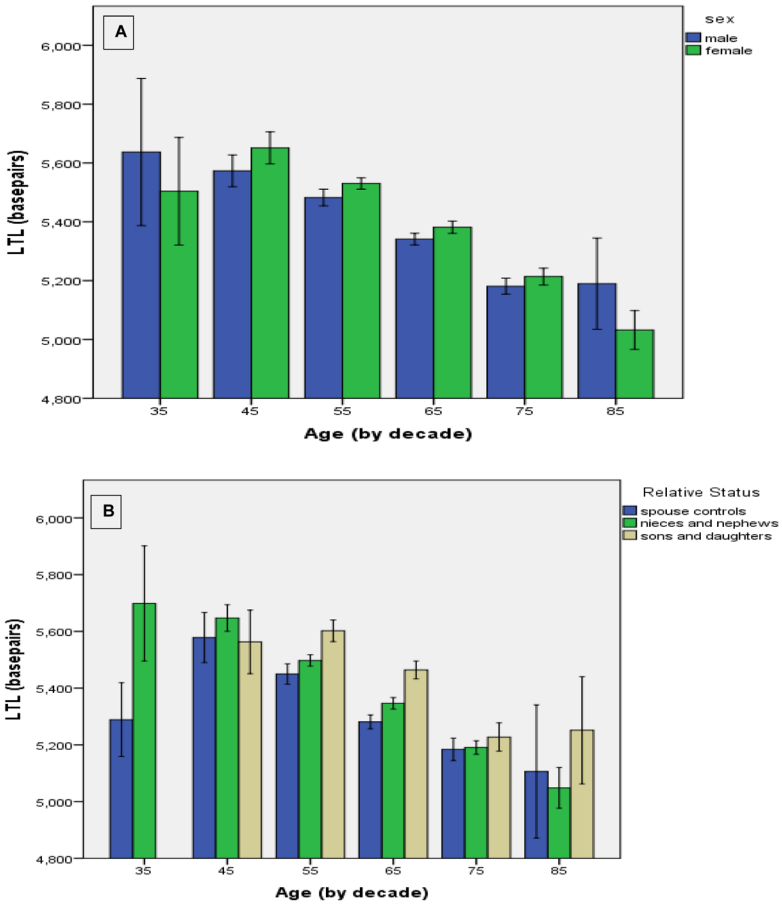

FIGURE 1. Relationship of Telomere Length to Sex and Family Relationship

Bar graphs of LTL versus age, aggregating participants within each decade of age: N = 16 (30–40 yr), 254 (40–50 yr), 1086 (50–60 yr), 1245 (60–70 yr), 397 (70–80 yr), 36 (80–90 yr). Panel A shows the relationship of mean LTL to gender, with males reasonably consistently having slightly shorter average LTL than females. Panel B shows the relationship of mean LTL to family relationship (relative) status, showing that sons and daughters have longer LTL than nieces and nephews, which in turn have longer LTL than do spouse controls. Error bars are standard errors (SE).

TABLE 1

Demographic Characteristics by Sex and Family Relationship

Characteristic	Offspring Spouse Controls	Offspring Relatives	Nephews/Nieces	Sons/Daughters
TOTAL GROUP, N	3040		2272	
Sample Size, N	768	2272	1548	724
Age, mean ± SD	60.9 ± 8.7	60.5 ± 8.7	59.9 ± 8.6	61.7 ± 7.2*
Sex, N (% Female)	360 (46.9)	1307 (57.5)	864 (55.8)	439 (60.6)*
Education, mean ± SD	12.0 ± 3.4	12.6 ± 3.0	12.4 ± 3.1	13.1 ± 2.7*
Ethnicity White, N (%)	760 (99.0)	2263 (99.6)	1543 (99.7)	720 (99.4)
Telomere Length, mean ± SD	5347 ± 525	5436 ± 532	5413 ± 501	5486 ± 589*
MEN, N	1373		965	
Sample Size, N	408	965	681	284
Age, mean ± SD	63.3 ± 8.1	60.5 ± 8.3	60.0 ± 8.7	61.7 ± 6.9
Education, mean ± SD	12.3 ± 3.1	12.8 ± 2.9	12.6 ± 3.0	13.3 ± 2.8
Ethnicity White, N (%)	404 (99.0)	961 (99.6)	679 (99.7)	283 (99.6)
Telomere Length, mean ± SD	5293 ± 440	5417 ± 561	5376 ± 519	5516 ± 641
WOMEN, N	1667		1307	
Sample Size, N	360	1307	867	440
Age, mean ± SD	58.2 ± 8.5	60.5 ± 8.2	59.8 ± 8.6	61.9 ± 7.3
Education, mean ± SD	11.7 ± 3.6	12.5 ± 3.1	12.2 ± 3.2	12.9 ± 2.7
Ethnicity White, N (%)	356 (98.9)	1302 (99.6)	864 (99.7)	439 (99.8)
Telomere Length, mean ± SD	5406 ± 602	5450 ± 530	5443 ± 485	5466 ± 554

Basic demographic and telomere length characteristics of offspring spouse controls and offspring. In the two right-most columns, offspring are separated into nephews/nieces, and sons/daughters. Comparisons were performed using ANOVA. Asterisks (*) mark significant unadjusted p-values ($p < 0.05$) for comparison of sons/daughters versus nieces/nephews.

TABLE 2

Likelihood of being in the highest tertile of telomere length in the offspring generation by total group and sex

Characteristic	N	N (%) in Highest Tertile of Telomere Length	OR (95%CI)	p
TOTAL GROUP				
Sons/Daughters	724	280 (38.7)	2.3 (1.7–3.1)	<0.00001
Nephews/Nieces	1548	522 (33.7)	1.5 (1.2–1.9)	<0.002
Spouse Controls	768	210 (27.3)	1.0 (reference)	
MEN				
Sons	284	123 (43.3)	2.3 (1.5–3.5);	<0.0002
Nephews	681	229 (33.6)	1.2 (0.9–1.7)	ns
Spouse Controls	408	105 (25.7)	1.0 (reference)	
WOMEN				
Daughters	440	157 (35.7)	2.6 (1.8–3.9)	<0.00001
Nieces	867	293 (33.8)	1.9 (1.3–2.7)	<0.001
Spouse Controls	360	105 (29.2)	1.0 (reference)	

Generalized Estimating Equations analysis, clustering by family group, analyzing relative status versus telomere length tertile (or sex-specific telomere length tertile), showing Odds Ratio (OR, and 95% confidence intervals), and p-value, for relative status adjusting for age, sex, race, and education. ns = not significant at level of 0.05.

TABLE 3

Heritability estimates by sex of older and younger generation.

	FULL MODEL			SIMPLE MODEL		
	N	**h^2**	**SE**	**N**	**h^2**	**SE**
PARENTS TO ALL OFFSPRING:						
Male Parents to All Offspring	3,404	0.674	0.046	3,502	0.626	0.045
Female Parents to All Offspring	3,568	0.607	0.042	3,653	0.592	0.041
MALE PARENTS:						
Males Parents to Male Offspring	1,855	0.654	0.067	1,925	0.593	0.064
Males Parents to Female Offspring	2,147	0.617	0.062	2,210	0.582	0.060
FEMALE PARENTS:						
Female Parents to Male Offspring	2,016	0.566	0.063	2,076	0.542	0.061
Female Parents to Female Offspring	2,311	0.529	0.054	2,361	0.530	0.053

Full model adjusts for demographic and environmental factors (see methods), while simple model adjusts only for demographic factors. Heritability (h^2) and standard error of heritability (SE) were estimated using SOLAR. For each analysis, N reflects total number of participants in each analysis (male or female parents plus offspring); numbers are not identical due to exclusion of subjects with missing covariates in the full model. Student's t- test was used to compare heritability estimates, and while each heritability was highly significant, none of the six subanalysis comparisons with respect to gender, were significantly different (i.e. whether male or female parents to all offspring, or whether female or male offspring) at the level of 0.05.